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# RELATIONSHIP OF PHYSICAL FITNESS, DEPRESSION AND MORTALITY IN A CARDIAC REHABILITATION COHORT

by

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A thesis submitted in partial fulfilment of the  
requirements for the degree of  
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# DECLARATION

**I declare that:**

- This thesis and the work presented in it are my own.
- This thesis has not been previously submitted for a degree or any other qualification.
- None of the work has been published before submission.

# THE RELATIONSHIP OF PHYSICAL FITNESS, DEPRESSION AND MORTALITY IN A CARDIAC REHABILITATION COHORT

## SUMMARY

The study aimed to establish whether levels of fitness and depression, or changes in those levels, in coronary heart disease patients are associated with survival time.

The cohort consisted of 2,714 coronary patients who were followed up for 13 [median 6.4] years after enrolment into a cardiac rehabilitation [CR] programme.

All participants underwent fitness testing and psychological assessment at the start of Phase III CR. These tests were repeated approximately 12 weeks later. Fitness levels were categorised into low, medium and high. Depression scores were divided into none, borderline and clinical depression. Primary endpoints were all-cause mortality and cardiovascular mortality.

At the end of the study period 16.6% of the cohort had died. The improvement in fitness over the 3 months of physical training was 16.8%. Fitness category improved in 33% of the cohort and deteriorated in less than 1%. Baseline fitness was predictive of all-cause and cardiovascular mortality with adjusted hazard ratios [HR] for low fitness of 2.83 [2.02,3.96] ( $p<0.001$ ) and 5.40 [3.36,8.69] ( $p<0.001$ ) respectively. Low fitness at the end of CR was predictive of mortality, HRs 4.23 [2.64,6.79] ( $p<0.001$ ) and 6.37 [3.37,12.0] respectively ( $p<0.001$ ). An increase in fitness amongst the least fit at baseline was associated with an 11% reduction in the risk of cardiovascular mortality [0.80,0.98] for each unit increase in fitness of 1ml/kg/min.

Baseline clinical depression was 4.6%. This had reduced to 1.1% by the exit assessment. Fitness levels were related to depression scores; the least fit participants were more likely to be depressed. The study showed an association between baseline clinical depression and all-cause and cardiovascular mortality, before adjusting for fitness, HRs 1.60 and 1.79.

Initial fitness and baseline depression are associated with prognosis in coronary patients who have attended CR. These findings may help target patients at risk in order to maximise treatments.

## ABBREVIATIONS

AACVPR	American Association of Cardiovascular and Pulmonary Rehabilitation
ACS	Acute Coronary Syndrome
BACR	British Association for Cardiac Rehabilitation
BDI	Beck Depression Inventory
BHF	British Heart Foundation
CABG	Coronary Artery Bypass Graft
CCU	Coronary Care Unit
CHD	Coronary Heart Disease
CI	Confidence Interval
CR	Cardiac Rehabilitation
CV	Cardiovascular
ECG	Electrocardiograph
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
ICD	International Classification of Diseases
IMD	Indices of Multiple Deprivation
MI	Myocardial Infarction
NOS	Not otherwise specified
NS	Non significant
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PTCA	Percutaneous Transluminal Coronary Angioplasty
RCT	Randomised Controlled Trial
RR	Relative Risk
SSRI	Selective Serotonin Reuptake Inhibitor



# Chapter 1

## Development of the Research Question

### *1.1 Introduction*

The patient recovering from an acute cardiac illness, for example a myocardial infarction<sup>i</sup>, needs help in two areas; the first to recover from the physical and psychological effects of the illness, and the second to ensure the best possible prognosis. This may be achieved by attending a cardiac rehabilitation [CR] programme, which incorporates exercise training together with approaches to health education, stress management and relaxation. CR programmes confer benefits in several equally important ways. Firstly, by providing individualised exercise prescriptions for each patient. Secondly, through rigorous management of their coronary risk factors, and thirdly, by inviting the patients and their partners to attend health education, stress management and relaxation classes during the time they spend in the programme. Finally, they are often the starting point for encouraging a lifelong adherence to healthier lifestyles and longevity.

The Basingstoke and Alton Cardiac Rehabilitation Programme was started in 1976 by Dr. Hugh Bethell, a general practitioner, and was one of the first programmes to be established in the United Kingdom.

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<sup>i</sup> myocardial infarction – heart attack



The CR programme was conducted in a local community sports centre and consisted of three sessions of exercise training each week for patients and their partners, supervised by one of the centre's exercise trainers. With research grants, charitable and National Health Service [NHS] funding I joined the team in 1979, initially on a part-time basis, as a chartered physiotherapist.

In 1992, I was appointed to a full-time NHS post to manage the CR service for Basingstoke District Hospital<sup>ii</sup>. Our approach to patient care has developed significantly over the years, modelled on schemes operating in North America (Wenger et al 1995) and our work has been, and continues to be, influential in the national development of secondary prevention programmes and rehabilitation services for patients with cardiac illnesses.

In order to monitor our interventions we routinely document a range of baseline assessment findings and outcome measures for all the patients during CR (Thompson et al 1997). It was this data, which we collected in the early years of our programme that became my inspiration for this thesis. The outcomes of one patient who attended CR for 3 months, made a lasting impression on me.

He was a gentleman who was currently being treated medically for clinical depression, and who enrolled in CR following his discharge from hospital with

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<sup>ii</sup> Basingstoke District Hospital - now re-named the Basingstoke and North Hampshire Hospital NHS Foundation Trust

a diagnosis of a myocardial infarction. He attended the programme regularly for 3 months. When he completed his rehabilitation we noted that not only had his level of fitness improved but also that he was less depressed than at the start of his CR with consequential reduction in antidepressant therapy. His case inspired me to look more closely at some of the outcomes we had begun to collect during CR and in particular the fitness and psychological data. I was curious to know whether initial fitness or changes in fitness as a possible result of exercise training, or baseline and changes in psychological scores would predict the prognosis of our CR patients.

In 1993 to facilitate data collection and with help from my family, I devised an electronic database for the storage of the patients' medical information, as opposed to recording the patient assessment data in paper format, which had been our traditional practice. One of my tasks, as clinical manager of the programme was, and still is, to ensure that all data collection on a range of patient observations was consistently recorded into the database that I had begun to develop. The baseline and outcome measures we continue to collect include before and after measures of physical fitness, psychological state, and coronary heart disease risk factor monitoring such as cholesterol levels, body mass index and blood pressure readings.

We also record occupational status, degree of perceived social support, and current medication as well as routine demographic data. Until now, this has been a unique activity within the field of CR. Most programmes in the United

Kingdom have not gathered data as a routine part of clinical practice. For instance, in 2000, only 8 out of the 302 programmes in the United Kingdom were able to provide outcome results relating to the exercise component of their CR programmes (Bethell et al 2004).

For the purpose of this thesis, the records of the patients with coronary heart disease in our database make up a cohort of nearly 3000 males and females who were invited to participate in CR between 1<sup>st</sup> January 1993 and 31<sup>st</sup> December 2002. In spite of the various new treatments that have become available during this time, which are discussed in Chapter 2, all of these patients have been exposed to a similar level and standard of CR, which has been delivered consistently over the ten-year study period. A range of data including measures of physical fitness and depression scores, the focus of this thesis, has been recorded on each participant.

The basis for my research on our patients is novel in the CR field for the following reasons:

1. The uniqueness of our patients' records. Our patients have all been observed as a part of routine practice in a clinical setting, as opposed to being participants in a randomised trial.
2. The data we have recorded therefore will have high external validity (Black 1996).
3. The participants in this study are the largest fully representative coronary heart disease population that has been studied within the



context of a CR setting to date. The majority of published research within the CR environment is concentrated on the younger male population with uncomplicated coronary heart disease.

## ***1.2 Purpose of the study***

Previous studies have found an association between levels of fitness and mortality in selected groups of coronary patients (Blair et al 1995; Kavanagh et al 2002; Kavanagh et al 2003) and some have also found a relationship between depression, coronary heart disease and survival (Ziegelstein 2001). Some researchers have looked at baseline fitness levels and depression within the context of CR and two studies have examined a change in fitness level and related it to survival in patients with pre-existing coronary heart disease who participate in CR (Fioretti et al 1988; Vanhees et al 1995). However, I have not identified any observational studies that have examined the changes in measures of physical fitness or depression scores in large numbers of male and female coronary patients, or the effect that these changes might have on outcomes from CR or survival of the patients.

The interaction between physical fitness and depression has also been little studied even though we know that treating clinically depressed myocardial infarction survivors with antidepressant medication, regardless of their level of fitness, does not appear to improve their survival (Strike and Steptoe 2002).



### **1.3 Study aim and objectives**

The aim of the study is to establish whether levels of fitness and levels of depression or changes in these levels of cardiac rehabilitation participants are associated with survival time.

The objectives of this research are to determine if the risk of mortality in our participants is predicted by:

1. A baseline fitness level at the start of CR and/or change in fitness level at the end of CR.
2. A baseline depression score at the start of CR and/or change in depression score at the end of CR.
3. An interaction between fitness baseline levels and depression scores.

The following chapter describes the background to my research and introduces the role that CR plays in treating patients with coronary heart disease.

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## Chapter 2

### Background to the study

#### **2.1 Coronary heart disease**

Cardiovascular diseases, which include diseases of the heart and circulatory system, are the leading cause of death in the United Kingdom. There are two main categories of cardiovascular disease, and they are coronary heart disease<sup>i</sup>, the focus of this study, and stroke. Coronary heart disease is the most common cause of death in western societies and a major financial burden to health care systems. The United Kingdom has one of the highest coronary death rates for its population in the western world. In 2003, 114,000 people died which represented one in five men and one in six women (Petersen 2005). In order to address the national death toll from coronary heart disease one of the Department of Health's [DOH] aims was to reduce cardiovascular deaths (i.e. deaths from coronary heart disease and stroke) in the under-75 year olds by two-fifths by the year 2010 (DOH 1999). The annual number of cardiovascular deaths including deaths from coronary heart disease has continued to fall year on year over the past decade mainly due to an improvement in treatments, and in particular the availability of cardio-protective medications such as statins<sup>ii</sup>. However, there are substantial variations in both the burden of, and premature death rate from, coronary heart disease across the United Kingdom. For example, the

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<sup>i</sup> For clarity throughout this thesis I will use the term coronary heart disease, although the same condition can also be referred to as coronary artery disease or ischaemic heart disease and the references I have selected may reflect this.

<sup>ii</sup> Statins – cholesterol lowering medications



premature death rate from coronary heart disease is far higher in Scotland and the North of England than in southern regions, in urban as opposed to rural areas, in Asians rather than Caucasians living in the United Kingdom, and in those who perform manual work compared with non-manual workers (Petersen 2005).

### **2.1.1 The aetiology of coronary heart disease**

Most heart disease, but not all, is a complex pathological process caused by atheroma, the patchy and gradual furring up of the endothelium<sup>iii</sup> of the coronary arteries in response to endothelial injury and inflammation. The formation of atheroma can start very early on in life, with streaks of lipid-rich material being deposited within the endothelium. Over time, these fatty deposits form into plaques, which encroach on the lumen<sup>iv</sup> of the artery reducing its diameter and resulting in a restriction of blood flow. Coronary atheroma may predispose to the formation of a thrombus or thrombosis<sup>v</sup> in one or more of the coronary arteries, reducing the lumen size even further.

A myocardial infarction occurs when the blood supply is severely occluded, and the segment of myocardium<sup>vi</sup> fails to receive adequate oxygenated blood. The chronic but more stable condition known as angina pectoris<sup>vii</sup> occurs when the coronary arteries are only partially blocked by atheromatous

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<sup>iii</sup> endothelium - innermost lining of an artery

<sup>iv</sup> lumen – diameter of an artery

<sup>v</sup> thrombosis – clot of blood

<sup>vi</sup> myocardium – heart muscle

<sup>vii</sup> angina pectoris – literally means a 'tight chest'

deposits. This condition gives rise to angina, a so-called strangling pain in the chest that is felt when the narrowed coronary artery does not allow sufficient oxygen-rich blood to reach the myocardium at any one time and as a result the myocardium becomes ischaemic. Angina may occur when the demand on the heart increases and the heart rate rises for example in response to emotion, physical exertion, in cold weather or after a heavy meal. Coronary heart disease can present in a variety of ways; as heart failure<sup>viii</sup> or an acute coronary syndrome<sup>ix</sup>, in addition to the terms I have already described.

### **2.1.2 Risk factors for coronary heart disease**

There is no single cause of atheroma although a cluster of risk factors has been identified which it is thought make certain individuals more prone than their counterparts to developing it. Some of the risk factors for coronary heart disease are unalterable, such as being male as opposed to female or inheriting a family history of heart disease, but others, for example being a smoker (Holm and Spencer 2000; Silagy 2000a; Silagy 2000b) being depressed (Glassman et al 2002), having a raised cholesterol level (de Lorgeril et al 1997) or leading a sedentary existence (Berlin and Colditz 1990) can be modified or controlled to improve outcomes for those with coronary heart disease.

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<sup>viii</sup> heart failure occurs when the heart fails to pump an adequate amount of blood around the body

<sup>ix</sup> acute coronary syndrome commonly refers to cardiac pain such as unstable as opposed to stable angina and is usually compatible with a myocardial infarction



### **2.1.3 Exercise and coronary heart disease**

The benefits of keeping active have been advocated for thousands of years. Hippocrates and his tutor Herodicus and other philosophers in the 4<sup>th</sup> and 5<sup>th</sup> centuries BC recommended exercise as a means of living long and healthy lives (Thompson 2004). Herodicus could be thought of as the first Sports Medicine Physician, allegedly encouraging his patients to eat a healthy diet and to keep fit by walking from Athens to Megara; a distance of about 70 miles. Over the years exercise has also been advocated for those with suspected heart disease. For instance in the 17<sup>th</sup> century the physician Heberden recorded that one of his patients was cured of his angina by regularly sawing wood for six months (Jay 2000).

Physical inactivity has therefore been linked to low levels of physical fitness and is considered a major risk factor for the development and progression of coronary heart disease (Blair et al 1996; Blair et al 1989; Paffenbarger et al 2001). The more physically active an individual is the greater their degree of fitness and the lower the risk for developing coronary heart disease (Berlin and Colditz 1990; Blair et al 1989). Moreover, the importance of the relationship between physical activity, physical fitness, cardiovascular health and survival has been well-established from epidemiological research carried out during the last 50 years. For example, studies of British workers (Morris et al 1953) compared the occupational activity of sedentary bus drivers versus the more physically active bus conductors, and also postmen, who spent up to 70% of their working day performing tasks that were aerobic in

nature, compared with deskbound telephonists and clerks. The main finding from these studies was that workers whose jobs were less physical were found to have suffered more heart attacks compared with the workers who were more active. However, statistical methods were less sophisticated at that time and the influence of confounders such as obesity or pre-existing coronary disease was not accounted for in the sedentary groups which may have affected the overall results (Batty and Lee 2004).

Other studies also confirmed that manual workers were less prone than non-manual workers to developing coronary heart disease and were also less likely to suffer a cardiovascular event. For instance, the heavy manual work performed by Californian longshoremen contributed to their longevity when compared with a group of office workers (Paffenbarger 1972). Twenty years later the relationship of physical activity in leisure time, as opposed to occupational exercise, and coronary heart disease was also established (Morris et al 1973). Nearly 17,000 male civil servants aged between 40-64 years who had sedentary jobs were asked to keep a diary of leisure-time activity for two days. Activity was considered vigorous if it reached an output of 7.5 kilocalories, which corresponded to performing heavy industrial work. This study showed that men who had a more active lifestyle and participated in vigorous leisure-time exercise at least twice a week reduced their risk of developing coronary heart disease by up to a third. Recent recommendations regarding the uptake of exercise for protection from developing coronary heart disease suggest that adults need only participate



in regular physical activity of a modest, rather than vigorous, intensity for about 30 minutes, but on most days of the week (Pate 1995).

Nonetheless the role of exercise as a method of secondary prevention of coronary heart disease within CR programmes has developed as a result of the findings from the early epidemiological studies. There are several reasons why exercise training plays a major part within CR. It enhances levels of physical activity, improves physical fitness and may also beneficially modify some of the other coronary risk factors, for example by lowering blood pressure, and helping with weight loss (Bethell and Mullee 1990; Miller et al 1997). In addition, it helps to regain self confidence (Marra et al 1985; Monpere et al 1988) and increases survival rates (Ades and Coello 2000; Pashkow 1993).

#### **2.1.4 Depression and coronary heart disease**

Depression is generally recognised to be a risk factor for cardiac mortality in people with coronary heart disease (Barth et al 2004; Carney et al 2003; Frasure-Smith and Lesperance 2005). Several researchers have shown the value of regular exercise for reducing depression in coronary patients during CR (Blumenthal et al 2004; Milani et al 1996; Turner et al 2002) and also in healthy but depressed adults who participate in exercise training programmes (Brosse et al 2002). Depression is a common finding within CR programmes (Turner et al 2003; Ziegelstein 2001) and its presence can complicate the pathway of the CR patient by influencing attendance (Deaner

2000; Glazer et al 2002; Larney 2002), compliance with medical treatments (DiMatteo et al 2000), and inducing excess fatigue (Beniamini et al 1997; McGowan et al 2004).

## ***2.2 Cardiac Rehabilitation Programmes***

### **2.2.1 The background and development of cardiac rehabilitation**

At the start of the 20<sup>th</sup> century Dr. John Garson from Hampshire (Garson 1909) published a textbook entitled Remedial Gymnastics for Heart Affections which encouraged people with heart disease to participate in exercise programmes. However, during most of the last century the fashion for exercise and beliefs about its benefits changed and patients with coronary disease were discouraged from taking any form of exercise for fear of provoking a further event or even dying. Patients who were admitted to hospital with a myocardial infarction remained in bed for at least six weeks. They were kept virtually immobile all day, and had their limbs moved passively by nurses and physiotherapists during the day to aid circulation.

In the 1950s, Levine and Lown invented the Armchair Management of patients admitted to hospital following myocardial infarction (Levine and Lown 1952). Patients were sat out of bed after the first few days in hospital, and carefully mobilised around the wards to combat the deleterious effects of prolonged bed-rest prior to being discharged home. This was a major breakthrough in the convalescence and rehabilitation of patients who had suffered an acute coronary event. During the next 10 years physicians in

North America (Hellerstein and Ford 1957; Hellerstein et al 1967) and in Israel, where CR first evolved, (Brunner 1968; Gottheiner 1968; Kellermann et al 1968) developed programmes of exercise rehabilitation specifically for restoring the health of coronary heart disease patients. By 1988 medically directed exercise was a core component of CR programmes in the United States. CR was much slower to develop in the United Kingdom, which has lagged behind other countries [Table 2:1]. However, over the past 35 years there has been a steady increase in the number of centres providing CR in the United Kingdom; the majority of CR programmes being implemented following the British Heart Foundation's pump priming initiative in the early eighties. In 1989, 99 programmes were reported to be offering comprehensive rehabilitation. This figure rose to 151 in 1995, 302 in 2000, at which time it was established that every acute hospital in the United Kingdom was running a programme or had access to a CR programme, and 332 in 2004 [Figure 2:1].



**Table 2:1 Key developments by decade in Cardiac Rehabilitation**

Adapted from H. Stokes (Stokes 2000)

	International	United Kingdom
1940s	Growing awareness of the dangers of bedrest	Prolonged bedrest & restricted mobility for cardiac patients
1950s	Early mobility and gradually increased physical activity	Prolonged bedrest & inactivity
1960s	Increasing emphasis on physical activity as well as psychosocial elements; organised CR; WHO <sup>x</sup> reports	Bedrest and slow mobilisation; no formal CR programmes in existence
1970s	Research into exercise training, psychosocial aspects, patient education, return to work, compliance. Growth in programmes and publications	Survey of CR 1970; major appraisal of CR by RCP <sup>xi</sup> & BCS <sup>xii</sup> ; a handful of programmes commenced; bedrest still recommended
1980s	Meta-analyses of exercise-CR published, professional organisations were formed	First trials of supervised exercise in the United Kingdom; 46/132 Health Districts providing CR; Pump priming of CR by BHF <sup>xiii</sup>
1990s	Evidence-based guidelines published; World Council formed	Less than half of Health Districts providing CR service; formation of BACR <sup>xiv</sup> ; national guidelines & audit standards developed 1994-1996
2000s		National Service Framework for Coronary Heart Disease published (DOH 2000). All health districts have access CR to service; 302 programmes registered.

<sup>x</sup> World Health Organisation

<sup>xi</sup> Royal College of Physicians

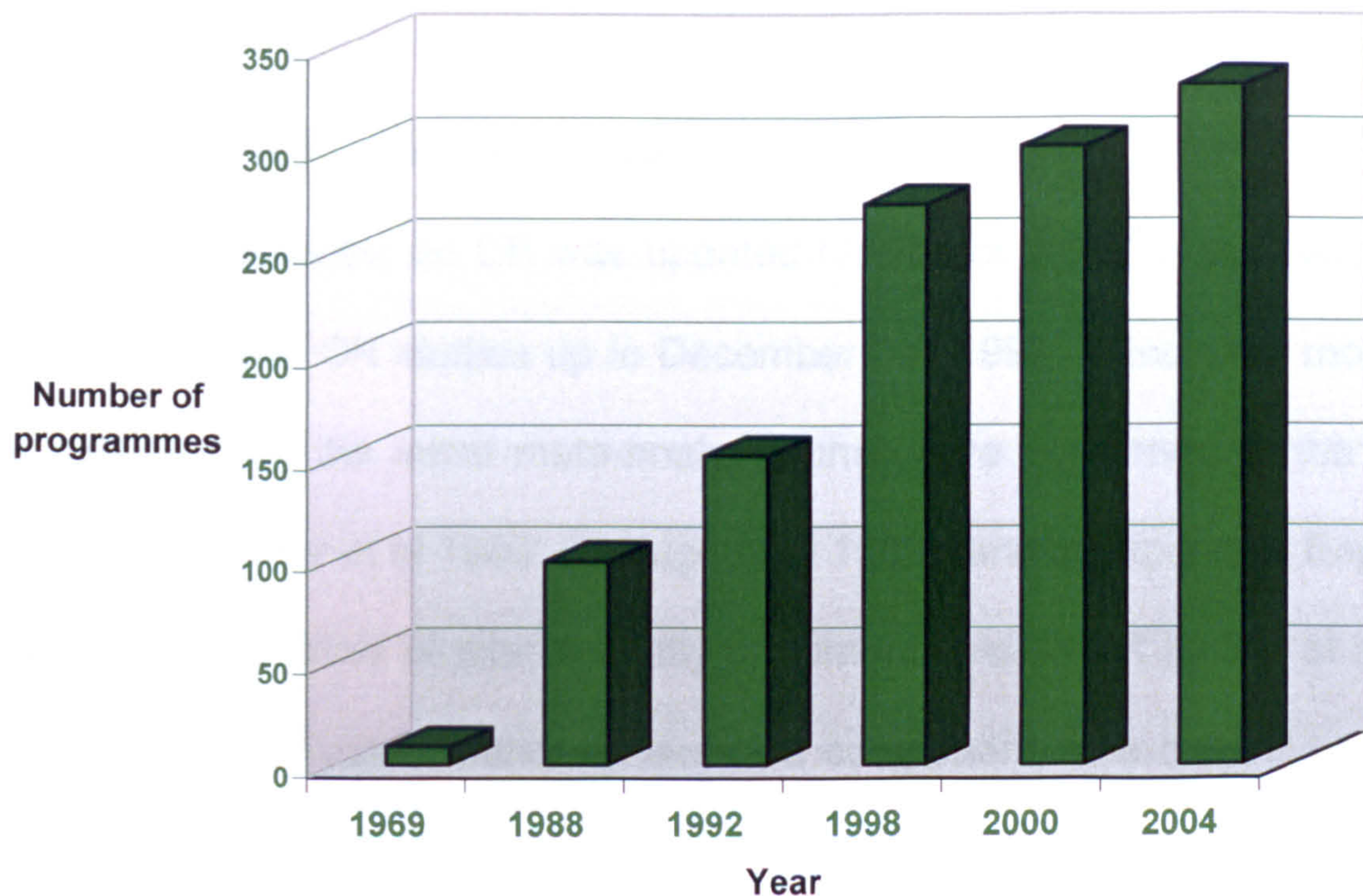
<sup>xii</sup> British Cardiac Society

<sup>xiii</sup> British Heart Foundation

<sup>xiv</sup> British Association for Cardiac Rehabilitation



**Figure 2:1 Growth in number of Cardiac Rehabilitation Programmes in UK**  
(BHF/BACR Annual Survey, Bethell et al. 2004)



Several comprehensive reports and systematic reviews were published between 1988 and 1999 (Goble and Worcester 1999; NHS 1998; Thompson 1995; Thompson et al 1996; Wenger et al 1995), which guided CR practitioners at the time in delivering CR services. However, some of the research material incorporated into earlier publications, including the systematic reviews and meta-analyses, has since been questioned because of the poor quality of some of the trials that had been included in the reviews. These tended to focus on small numbers of male coronary heart disease patients, rather than women, and in younger as opposed to older age groups (Ebrahim and Davey Smith 1996; NHS 1998). By the end of the nineties the



effectiveness of the various components of CR either singly or in combination were still relatively unclear which prompted production of a Cochrane review of CR that included an exercise component (Jolliffe et al 2000).

### **2.2.2 Systematic reviews on cardiac rehabilitation**

This Cochrane review on CR was updated (Jolliffe et al 2003) and reported on the majority of CR studies up to December 31<sup>st</sup> 1998. It included most of the studies from the initial meta-analyses that were performed in the late eighties (O'Connor et al 1989; Oldridge et al 1988), and incorporated English and non-English trials of exercise only or comprehensive CR lasting at least six months that involved either an exercise component, or a combination of exercise and psychological intervention - referred to as 'Comprehensive' CR. The trials were subdivided on the basis of differing interventions. There were a total of fifty-one trials involving 8,440 patients included in this review. All patients in the studies had suffered an acute myocardial infarction or had coronary artery bypass grafts, percutaneous coronary interventions or been diagnosed with other forms of coronary heart disease, such as angina. Nearly all of those recruited to the studies were middle-aged males, who were considered to be at a low risk for sustaining a further cardiac event. Females with coronary disease were poorly represented. All-cause and coronary mortality, nonfatal myocardial infarction or new cardiovascular events, revascularisation and health related quality of life were the main outcome measures. Some of the trials did not measure all these outcomes of interest, however, the Cochrane review demonstrated that over a three



year period cardiac mortality was reduced by 31% for both exercise only or comprehensive CR groups [Odds Ratio [OR] 0.69, 95% Confidence Interval [CI] 0.51,0.94]. All-cause mortality was reduced by 27% [OR 0.73, 95% CI 0.54,0.98] in the exercise only group but not in the group that had received comprehensive CR [OR 0.87, 95% CI 0.71,1.05]. These findings differed from those obtained from the original meta-analyses performed in the late eighties (O'Connor et al 1989; Oldridge et al 1988), which had shown statistically significant reductions in cardiac and all-cause mortality of approximately 20–25% for the patients who had received CR which included an exercise component. It was not clear from the Cochrane results whether exercise only or comprehensive CR was the more effective intervention. Moreover, interpretation of the results is limited by the exclusion of some patients from the studies, which may have benefited from participating in CR, such as those who were older, had greater co-morbidity or who were female. Had these categories of patients been included a more realistic picture of the effectiveness of CR in terms of longevity and survival may have resulted. In addition, there were no analyses performed relating to the psychological components of CR because evidence for the effect of CR on depression, or quality of life, was only available from the four studies that had used a variety of disease-specific questionnaires.

However, psychological components of CR are considered an equally important part of the rehabilitation process (Lewin et al 1992) and a Cochrane review of psychological interventions for coronary heart disease

has been published which includes outcomes for females, the elderly and revascularisation patients in the analyses (Rees et al 2004). The results from the thirty-six trials that Rees and colleagues examined showed that psychological interventions, at least within the CR environment, had no effect on either cardiac or total mortality, although some of the trials did show reduced levels of depression after attendance at CR. This review is discussed in greater detail in Chapter 7.

Taylor and colleagues, with support from the Cochrane Heart Group, have published a meta-analysis and systematic review of the effectiveness of exercise-based CR which updates the earlier Cochrane reviews of CR (Jolliffe 2000; Jolliffe 2003). Taylor et al's review included 48 randomised controlled trials of CR that were published through to March 2003 [Table 2:2] (Taylor et al 2004). Although the number of studies was less than previously reported by the Cochrane reviewers, a greater number of patients were represented [8,940 compared to 8,440]. Thirty-two of the forty-eight trials focused on myocardial infarction patients, with females accounting for 20% of the total percentage of patients that were studied. This was in contrast to the Cochrane review where only 4.4% and 11% respectively of female participants in the exercise only or comprehensive CR trials had been included. The results from Taylor's review suggest that CR is effective in reducing all-cause mortality [OR 0.80, 95% CI 0.68,0.93] and cardiac mortality [OR 0.74, 95% CI 0.61,0.96] independent of the diagnoses of the participants and the type of multi-disciplinary rehabilitation they had received.



The reviewers found no difference in mortality between exercise-based CR versus comprehensive CR or by the exercise dose - i.e. the type, intensity, frequency and duration of sessions. In addition, they reported that the attendance rates of the patients at CR did not have any effect on subsequent occurrence of nonfatal myocardial infarction.

**Table 2:2 Selected characteristics of the trials** (Taylor et al 2004)

Characteristic	Number	(% or Median <sup>ψ</sup> range)
<b>Exercise only trials</b>	19	(39) *
<b>Sample size</b>	112	(37-1479 patients)
<b>Publication date</b>		
1970-1979	2	(4)
1980-1989	17	(35.5)
1990-1999	21	(44)
2000-2003	8	(6.5)
<b>Study location</b>		
Europe	30	(63)
North America	13	(27)
Asia/Australia	5	(10)
<b>Sex</b>		
Men only	21	(44)
Women only	1	(2)
Both	26	(52)
Unspecified	1	(2)
<b>Age, years</b>	55	(48-71)
<b>Diagnosis</b>		
Post myocardial infarction	32	(67)
Revascularisation only	8	(6.5)
Both	8	(6.5)

A major limitation with the research carried out to date is that it continues to report mainly on CR following myocardial infarction as opposed to CR as an intervention after revascularisation or for those with stable angina. Only some of the trials include data on females and the elderly. On the basis of the

<sup>ψ</sup> Median of study means

\* 49 trials of which one trial included both exercise only CR and comprehensive CR arms



evidence that was produced prior to the publication of the three systematic reviews I have discussed above, the National Service Framework for Coronary Heart Disease suggests that CR should become an essential and integral part of the secondary prevention plan for the majority of coronary patients (DOH 2000).

Evaluation of modern CR interventions indicates that they may provide a variety of benefits for attendees, which include physical, psychological and prognostic gains as well as reducing long term cardiac morbidity and improving survival (AACVPR 1999; Coats et al 1995), although the mechanisms responsible for these improvements remain unclear (Stokes 2004; Taylor et al 2004). The following section explains how CR programmes set about achieving these benefits.

### **2.2.3 The process of cardiac rehabilitation**

CR is the process by which patients with cardiac disease, in partnership with a multi-disciplinary team of health professionals, are encouraged and supported to achieve and maintain optimal physical and psychosocial health (SIGN 2002). The World Health Organisation describes CR as:

“The sum of activities required to influence favorably the underlying cause of the disease, as well as to ensure the patients the best possible physical, mental and social conditions, so that they may, by their own efforts, preserve or resume when lost, as normal a place as

possible in the life of the community. Rehabilitation cannot be regarded as an isolated form of therapy but must be integrated with the whole treatment of which it forms only one facet” (WHO 1993).

The centrepiece of CR is often an exercise programme. The uptake of regular aerobic-type exercise, whether supervised or not, has a favourable effect on many of the coronary risk factors. For instance it may lower blood pressure (Whelton et al 2002), alter cholesterol profiles by raising the levels of high-density lipoproteins in the blood, (Kraus et al 2002) reduce obesity over time when coupled with sound dietary advice (Ross et al 2000) and alleviate stress by reducing anxiety and depression (Rozanski et al 2005). CR involves a variety of other interventions as well as exercise: health education, stress management and relaxation therapy, counselling, self-help manuals, home exercise programmes and risk factor monitoring. The medically supervised exercise programme is the backbone of the rehabilitation process, striving to turn previously sedentary patients and often their partners into habitual exercisers.

#### **2.2.4 The evidence for cardiac rehabilitation**

The original CR programmes that developed in the sixties and seventies (Bethell et al 1983; Carson et al 1982; Kavanagh and Shephard 1973) concentrated on physical fitness and physical activity following myocardial infarction, enrolling mainly young white collar males to participate in regular supervised exercise sessions to aid their recuperation. Moreover, results from the early randomised controlled trials of exercise-based CR sought to establish the effectiveness of CR as an intervention for patients who had suffered a myocardial infarction (Bobbio 1989; O'Connor et al 1989; Oldridge et al 1988). Subsequent systematic reviews and meta-analyses (Jolliffe et al 2000; Wenger et al 1995) address other components of CR as well as exercise training, to include psychological and educational interventions and greater numbers of patients with other manifestations of coronary heart disease. Two systematic reviews have shown CR is an effective intervention for patients with coronary heart disease (Jolliffe et al 2003; Taylor et al 2004).

#### **2.2.5 The phases of cardiac rehabilitation**

In the United Kingdom the process and time-course of CR has been divided into four separate but overlapping phases (Coats et al 1995), although the theme of secondary prevention may start with rehabilitation and prevails as a continuum throughout all four phases of rehabilitation (Thompson and De Bono 1999).

**Phase I** relates to the period when the patient is in hospital – usually having had a myocardial infarction, an episode of unstable angina pectoris, or having



undergone revascularisation; either coronary artery bypass grafting [CABG] or angioplasty<sup>xv</sup>. Revascularisation is performed to alleviate the symptoms of coronary heart disease and to improve quality of life. The first phase of CR usually lasts for up to 5 days, but with the advent of earlier investigations during an acute cardiac event such as undergoing angiography<sup>xvi</sup>, the duration of the time in hospital may now only last 1-2 days. Patients and their families are given help to understand the nature of their illness by specialist cardiac nurses and are given going home advice or a self-help manual to assist convalescence.

**Phase II** refers to the period immediately after discharge from hospital, when the patient returns home and comes under the care of the community's primary health care team. The duration of this phase is variable and often lasts for 2-4 weeks until the exercise component begins. It used to be dependent upon several factors which includes: the formation of scar tissue in the myocardium, currently not so relevant as new technologies such as rescue or primary angioplasty have become available, the healing of the sternum for the surgical patients, the patient's ability to reach the rehabilitation centre and the availability of hospital transport. The advice received in hospital is put into practice and the patient may receive telephone support or a visit from a CR team member or the cardiac nurses from the hospital during this time.

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<sup>xv</sup> angioplasty is a procedure performed to reduce angina/chest pain by opening up the lumen of the artery. It is also referred to as 'percutaneous transluminal coronary angioplasty'. A stent is inserted to help to maintain the diameter of the newly re-opened coronary artery.

<sup>xvi</sup> angiography is an invasive procedure which involves the injection of radio-opaque dye into the blood stream to show up the coronary arteries

**Phase III** of rehabilitation concentrates on active physical recovery provided through an individualised and incremental exercise prescription together with continuation of lifestyle advice and the risk factor monitoring which was provided in the first two phases. The patient returns to the hospital as an outpatient or to a suitably equipped leisure centre or gymnasium in the community to participate in an exercise and health education programme. This phase usually lasts for between 6-12 weeks in the United Kingdom, although it may last for much longer especially for patients who are in heart failure or who remain unwell.

**Phase IV** involves compliance with a healthy lifestyle and risk factor control in the long term. The patients reach this phase when they have achieved their personal physical and psychological rehabilitative goals, are asymptomatic and confident about being physically active, and independent of medical supervision. Potentially they remain in Phase IV for life, unless succumbing to further cardiac illness or disability, which requires them to return to one of the earlier phases of rehabilitation.

### ***2.3 Changing recruitment to cardiac rehabilitation***

The type of patients enrolled in CR programmes has changed during the past two decades, and there are several reasons that may explain this. The definition of an acute myocardial infarction has altered over time. Formerly there were three criteria set down by the World Health Organisation that confirmed the diagnosis: a rise and fall of cardiac enzyme levels during the first three days in hospital, changes on an electrocardiograph [ECG] trace



involving development of Q waves<sup>xvii</sup>, and symptoms of chest pain (Tunstall-Pedoe et al 1994). These patients were eligible for CR because they had suffered a true heart attack and it is these criteria that were used when identifying the myocardial infarction patients in this study.

The term myocardial infarction has been redefined. It was recently realised that this definition excluded many patients who had in fact suffered an infarction. From 2005 onwards, patients admitted to hospital with symptoms of unstable angina, with or without a myocardial infarction, are diagnosed with an acute coronary syndrome. An acute coronary syndrome is considered to be a spectrum of clinical conditions which includes unstable angina, ST segment elevation<sup>xviii</sup> or non-ST segment elevation myocardial infarction and chest pain. Biochemical markers, for example, the cardiac enzyme Troponin T or Troponin I are measured to detect the smallest amounts of myocardial necrosis (McKenna and Forfar 2002) and thus confirm a diagnosis. Troponin concentration is measured in nanograms per millilitre [ng/ml] and is not detected in the blood of healthy people. An acute coronary syndrome may be diagnosed when the Troponin T level is equal or greater than 1.0ng/ml or in the case of Troponin I greater than 0.5ng/ml. However, an acute coronary syndrome is not diagnosed on troponin levels alone because elevated troponin levels are also seen in pneumonia,

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<sup>xvii</sup> Q waves – There are five deflections on the familiar Electrocardiograph [ECG] which are labelled PQRST. A Q wave indicates a full thickness myocardial infarction

<sup>xviii</sup> ST segment elevation - When the ST segment of the ECG is elevated it helps to diagnose a myocardial infarction

pulmonary embolus, myopericarditis, myocardial contusions, renal failure and arrhythmias.

Many patients undergo surgical procedures for revascularisation in the form of either coronary artery bypass grafts or percutaneous coronary interventions such as angioplasty and stenting. In relation to attendance at CR the type of procedure that each patient receives is important for several reasons. The less invasive procedures enable the exercise component of CR to be started sooner, and for some patients a more aggressive approach to exercise may be considered than had been possible in previous years. Recovery time including a period of convalescence following a less invasive intervention should be swifter, although no research published to date confirms this.

Although many patients in this study underwent percutaneous coronary interventions, none were treated with the minimal invasive technology available for coronary artery bypass patients; this has only recently become available to our coronary patients. Most of the patients in this study had surgical interventions between one month and up to 2 years after their index coronary event.

With the accessibility of new treatments the prognosis of patients diagnosed with coronary heart disease has improved. These innovations include medications that help to limit disease progression such as lipid lowering



therapy for reducing cholesterol levels, the rigorous use of angiotensin converting enzyme inhibitors, post infarction  $\beta$  blockade and anti-platelet therapy, all of which help the secondary prevention of coronary heart disease. As a result of government targets and milestones more patients are offered CR programmes and the aftercare in the community has become more effective.

In the randomised controlled trials and meta-analyses of CR performed between the 70s and up to the late 80s the focus was mainly on young male myocardial infarction patients (O'Connor et al 1989; Oldridge et al 1988). Current CR participants are older because life expectancy has increased due to improved treatments for their medical conditions and also because the need to make CR programmes more accessible to elderly people has been recognised. Older people are beginning to be better represented in recent studies (Ades 1999; Ahto et al 1997; Austin et al 2005; Fattirolli et al 1998). The number of females being recruited into CR has grown due in part to an improvement in detecting coronary heart disease in women. Females were commonly misdiagnosed in the past because their symptoms were often less obvious and not stereotypical (Miller 2002).

## **2.4 Summary**

Most published studies of coronary heart disease within the CR population have involved small numbers of patients who have sustained uncomplicated myocardial infarctions, and for whom the prognosis is good (Jolliffe et al

2003). Long term outcome data related to coronary heart disease patients who access CR programmes are limited and some data are skewed by including these selected patient populations. For example most research in this field of medicine has focused on younger, male patients who were enrolled in the early CR programmes during the 70s (Carson et al 1982; Mayou et al 1981; Oldridge et al 1983). On the other hand, the main strength of my observational research lies in the large number of patients studied and their wide spread of age, fitness, co-morbidity and cardiac performance.



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# **Chapter 3**

## **Review of the Literature**

### **Introduction and Methods**

#### ***3.1 Structure of the review***

The literature review is divided into 5 chapters of which this chapter provides an introduction to the following 4 chapters in my thesis. In this first chapter, I describe the search strategy I used to select the studies included in my thesis as well as the criteria I adopted to locate the papers and publications that I finally chose for inclusion.

Chapter 4 focuses on what is known about physical fitness and changes in physical fitness as predictors of progression in coronary heart disease and includes a definition of physical fitness and physical activity.

In Chapter 5 I examine the epidemiology of coronary heart disease progression and depression. In this chapter, I define clinical depression and focus on the role of depression as a risk factor in coronary heart disease.

Chapter 6 describes the pathophysiological mechanisms associated with coronary heart disease and depression. Finally, in Chapter 7 I discuss the role of antidepressant therapy and psychological interventions in people with

coronary heart disease. This chapter includes a section on the Cochrane Review of psychological interventions for coronary heart disease (Rees et al 2004) and also examines studies of depression and exercise within the CR environment.

My initial searches used the databases illustrated in Table 3:1.

**Table 3:1 Databases accessed in my initial searches**

Database	Dates	Comments
Dialog-DataStar		Access to databases marked ¢ plus DH data, Kings Fund & Allied Health Professionals database
Science Citation Index	1981 to date	Covers over 2,500 medical journals
¢Medline	1951 to date	Bibliographic database of the National Library of Medicine
¢PubMed		The National Library of Medicine’s search service of which Medline is a part
¢Cinahl	1982 to date	Cumulative Index to Nursing and Allied Health Literature
¢Embase	1974 to date	Biomedical and pharmaceutical databases world wide
¢PsychINFO	1806 to date	Psychological resources database
The Cochrane Library		Updated evidenced – based health care
TRIP		Turning Research into Practice – an evidenced base database
Zetoc	1993 to date	Access to the British Library’s electronic table of contents
The National Research Register		To locate on-going research projects



The key words used in each electronic database for the searches included the following selection:

- Cardiac
- Cardiovascular
- Coronary
- Coronary heart (artery) disease
- Coronary artery bypass graft
- Depression
- Exercise
- Ischaemia
- Ischaemic heart disease
- Longitudinal/cohort studies
- Meta-analysis(es)
- Mortality
- Myocardial infarction
- Percutaneous transluminal coronary angioplasty
- Physical activity
- Physical fitness
- Randomis(z)ed, controlled trial(s)
- Rehabilitation
- Reinfarction
- Revascularisation
- Review
- Secondary prevention
- Survival

I used these words both singly and in combinations with each other. Wild card symbols [\*] were used to truncate words that had similar roots but different endings – such as 'ischaemic' and 'ischaemia' and also to differentiate between words that were spelled in American or English as

illustrated in the Table 3:2. When a search produced too many references [over 400 at any one time] I limited the parameters of the searches to produce a more manageable selection.

**Table 3:2 Example of search terms**

Term	Number of references retrieved for review <sup>1</sup>
Depression+ischaemia+survival	626
Depression+ischaemia+mortality	1109
Exercise+ischaemia+survival	1287
Exercise+ischaemia+mortality	2154
Cardiac+rehabilitation+fitness	331
Cardiac+rehabilitation+ myocardial infarction	1688
Cardiac+rehabilitation+ revascularisation	19

<sup>1</sup> Some references may be duplicated in 2 or more databases

I located most of my references by utilising the online pre-configured connection to a bibliographic software management programme. Retrieving references from a remote database such as PubMed was far easier than using traditional structured methods of searching. I chose PubMed as my main database because access was free and did not require a password. It was possible to view publications using a variety of headings, such as authors, year, or topics. I then browsed the title of each article and the abstract, when available, and downloaded potential references into a library created for this thesis. It was possible to obtain full 'pdf' texts using this method from many journals by using the URL link that was displayed. I

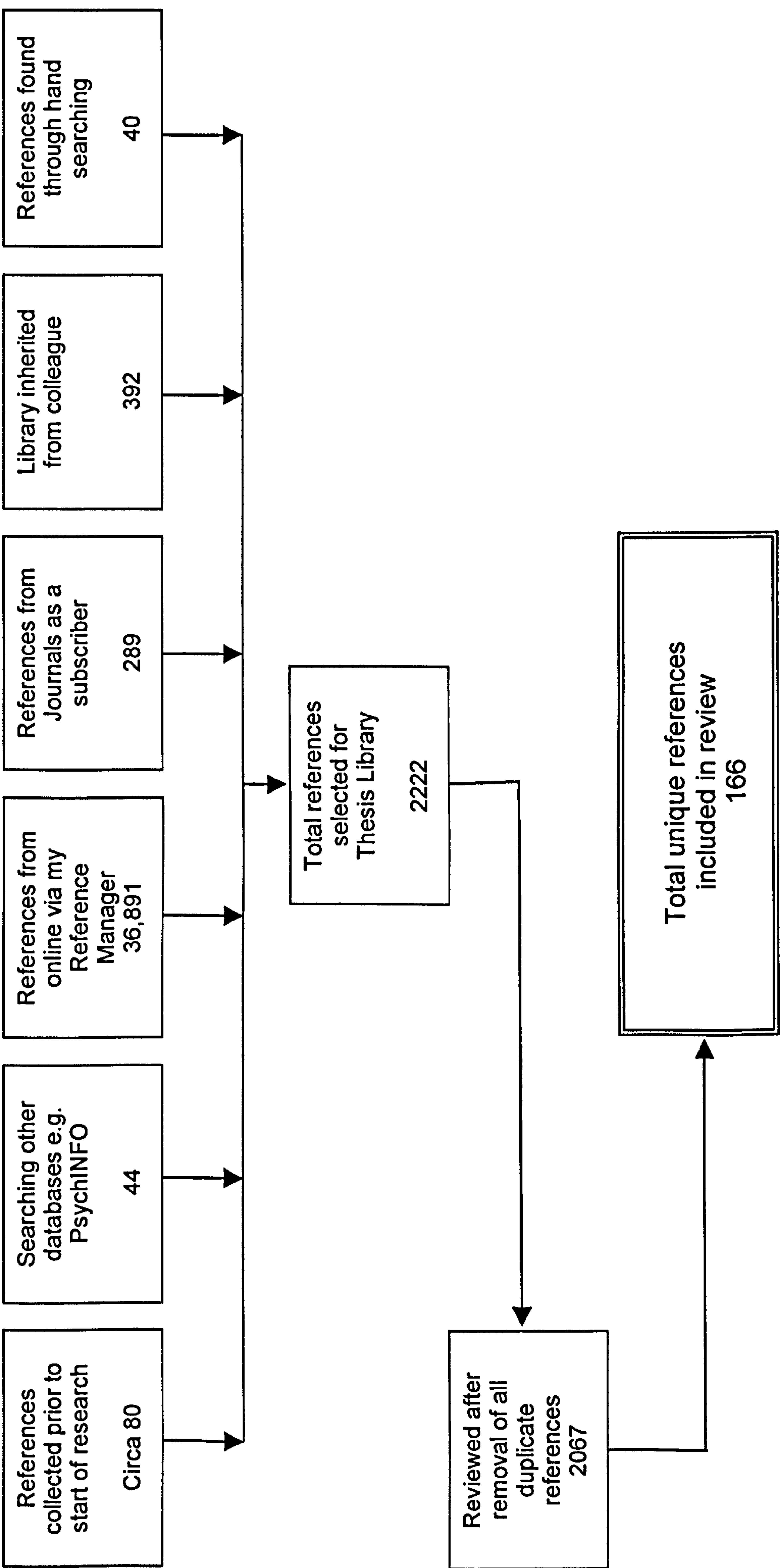
deleted duplicate and triplicate references from my thesis library on a regular basis.

One source of material was through access to the World Wide Web and the Internet. I registered online for notification of newly published journal articles relevant to my research, selecting suitable articles which I subsequently obtained using my reference manager, as described above. Another source of literature was from the journals I subscribe to on a regular basis. These are *Heart*, *The Journal of Cardiopulmonary Rehabilitation*, *The European Journal of Cardiovascular Prevention and Rehabilitation* and the *British Journal of Cardiology*. Additional references were obtained through hand searching papers that I already had prior to starting this research project, and by scanning the bibliographies and reference lists of the papers I had collected for assessment. I identified key authors and experts in the field of my thesis, and approached them in person at conferences or via email to request specific papers. All those I approached, without exception, sent me a copy of their publications. The final number of references is shown in Figure 3:1.

All relevant references, together with their abstracts, when available, were downloaded from the Internet or transcribed manually into my reference manager (Thomson 2002). After removal of all duplicate and triplicate entries, a total of 166 unique publications were selected for inclusion in this review.



**Figure 3:1 References selected for my Review of the Literature**



### **3.1.1 Selection of the studies**

I have limited my research to aspects of coronary heart disease. There are three reasons for this decision. Firstly, by excluding other manifestations of cardiovascular disease, such as peripheral vascular disease or cerebral vascular disease, I have been able to concentrate on the vast amount of literature that is accessible on coronary disease alone. Secondly, the patients in my cohort joined the CR programme because of their coronary pathology, although they may also have presented with a significant degree of systemic cardiovascular co-morbidity. Thirdly, specific rehabilitation techniques used to treat patients with either cerebrovascular or peripheral vascular disease are markedly different from the methods we use to rehabilitate coronary patients. For example, patients with peripheral vascular disease are encouraged to walk through the pain of claudication, felt in their calf muscles to stimulate the formation of collateral circulation (Skinner and Strandness 1967). For coronary patients it is contraindicated to exercise above the ischaemic anginal threshold for fear of making the myocardium ischaemic and provoking life-threatening ventricular arrhythmias.

I used the following criteria to select the publications that were included in this literature review:

Publications were written in English, and  
related to coronary heart disease

included physical fitness, and/or depression, and mortality in people with pre-existing coronary heart disease

involved CR as an intervention that addressed either exercise or the psychological sequelae of coronary disease

looked at physical fitness, and/or depression with reference to mortality or morbidity as outcome measures

Therefore the review includes results from research performed within the context of CR programmes such as ours; these being likely settings for studying fitness and depression in relation to the management of patients with coronary disease. It also includes literature from the non-CR environment.



## Chapter 3: References

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## **Chapter 4**

# **Physical fitness and changes in physical fitness as predictors of progression in coronary heart disease**

### ***4.1 Introduction***

Epidemiological studies have demonstrated an important association between physical activity, physical fitness, cardiovascular health and survival (Blair et al 1989; Kavanagh et al 2002; Kavanagh et al 2003; Morris et al 1973; Morris et al 1953; Morris et al 1966; Paffenbarger 1972). It is well-established that regular physical activity increases exercise capacity and improves physical fitness and also confers a variety of other health gains, such as reducing the risk of stroke (Lee and Paffenbarger 1998; Wannamethee and Shaper 1992), some cancers (Giovannucci et al 1995) and diabetes (Haapanen et al 1997). The more physically active an individual is, the greater their degree of fitness and the lower the risk for developing coronary heart disease (Berlin and Colditz 1990; Blair et al 1989). Even small improvements in fitness appear to reduce mortality (Erikssen et al 1998), but more vigorous exercise regimes have a greater effect in populations with or without cardiovascular diseases (Blair et al 1996; Vanhees et al 1994). The mechanisms through which biological and clinical benefits of physical activity and physical fitness are mediated are not clear (Vanhees et al 2005) and sometimes seem contradictory (Hambrecht et al 2000).

## **4.2 *Physical fitness and physical activity***

Physical fitness and physical activity are significant factors in both the prevention and treatment of coronary heart disease. Physical fitness is defined as:

“The capacity to meet the present and potential challenges of life. Physical fitness is a set of attributes that persons have or achieve that relates to the ability to perform physical activity” (CDC 1996a)

There are a number of health related components to physical fitness. These are flexibility, muscular strength, muscular endurance, explosive strength, balance, speed and cardiorespiratory fitness (Vanhees et al 2005). Cardiorespiratory fitness, also referred to as exercise capacity, endurance fitness or aerobic power, is the ability of the body's circulatory and respiratory systems to use oxygen during steady state exercise. Poor cardiorespiratory function or low levels of fitness are particularly important aspects of total physical fitness because they are associated with both the development and progression of coronary heart disease.

Aerobic<sup>i</sup> exercise and physical activity are associated with physical fitness because the uptake of exercise or becoming more active helps to improve fitness levels (Thompson et al 2003). Physical activity is:

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<sup>i</sup> Aerobic means with oxygen, and refers to the utilisation of oxygen by muscles to produce energy. Aerobic exercise increases stamina – our ability to keep going when performing exercise such as brisk walking or jogging, cycling, rowing or swimming.



“Bodily movement that is produced by the contraction of skeletal muscle and that substantially increases energy expenditure” (CDC 1996b).

Examples of physical activity are found in all the routine activities we perform daily, for example household jobs, shopping and work

For health-related fitness, adults should participate in regular physical activity of a ‘modest’ intensity for about 30 minutes on most days of the week (Pate 1995) although results from the earlier epidemiological studies found that vigorous, as opposed to modest exercise, afforded greater cardiac protection (Blair et al 1996). High levels of physical fitness are sustained by greater levels of physical exertion. Conversely, a reduction in exercise habit for whatever reason will decrease levels of physical fitness. Exercise training is capable of improving physical fitness in those with or without coronary heart disease (Bethell 1987; Dugmore et al 1999; Shoenfeld et al 1980).

The Health Survey for England (DOH 2004) found that only 37% of males and 25% of females reported doing the recommended amount of exercise weekly. In the over 75 year old age group the figures were smaller, with only 7% of males and 4% of females achieving the suggested targets. The earlier Allied Dunbar Survey had measured fitness objectively via exercise treadmill testing as opposed to questionnaires (The Sports Council 1992). This survey found that one third of men and two thirds of women were unable to walk up

a 5% gradient at 3.00mph without exceeding 70% of their maximum heart rate, which indicated a low level of physical fitness within their sample.

### ***4.3 Measuring physical fitness and physical activity***

It has been suggested that physical fitness and physical activity should be considered as separate and independent characteristics (Myers 2005; Williams 2001). They are measured in a variety of ways. Data on physical activity is collected from physiological responses to exercise - i.e. heart rate, the use of motion sensors such as pedometers and accelerometers, or via self-reported diaries or questionnaire surveys. However, these methods are difficult to quantify accurately (Haskell and Kiernan 2000). Measuring physical/cardiorespiratory fitness, rather than physical activity, may be a better marker of cardiovascular state (Myers et al 2002; Vanhees et al 2005).

The measurement of physical fitness is not straightforward because it embraces several components. While some publications refer to cardiorespiratory fitness, others use the term physical fitness to describe only the cardiorespiratory component of total physical fitness. For the purpose of this thesis, I shall refer to cardiorespiratory fitness as physical fitness, unless it is important to differentiate between the two terms.

An integral aspect of clinical assessment at the start of CR is the recording of current fitness levels. Various ways of measuring physical fitness are available. The most accurate way uses direct measurement of oxygen



uptake [ $\text{VO}_2$ ] by analysis of expired gas. The rate of oxygen consumption during maximum exercise [ $\text{VO}_{2\text{max}}$ ] is the gold standard measure of physical fitness, but does require expensive equipment to perform.

Cycle ergometry, usually used in field tests, or treadmill exercise testing, under laboratory conditions (Shephard et al 1968) are two methods for determining  $\text{VO}_2$  (Andersen et al 1971).  $\text{VO}_2$  can be predicted from the workload performed during cycling or walking on the treadmill and is expressed as maximum, peak or symptom limited. In practice, most cardiac patients are tested to a level below maximum [sub maximum] because of the development of symptoms [symptom limited]. Various protocols have been designed and standardised for exercise testing using a treadmill, cycle ergometer, step test or shuttle walk. Some researchers express exercise rate in watts, [one watt being equivalent to one joule of energy per second], whilst others use METS [one metabolic equivalent is the consumption of 3.5 millilitres of oxygen per kilogram per minute] to reflect the energy requirements for certain activities.

#### ***4.4 Strategy for searching and selection of studies***

This chapter focuses on physical fitness and the effects of changes in physical fitness in relation to disease progression in people with coronary heart disease. To locate the references for this section of my literature review, I searched systematically papers on physical fitness and mortality and the pathology of cardiovascular, as opposed to coronary heart disease.



My inclusion criteria were studies that incorporated a baseline measure of cardiorespiratory fitness or reported on changes in levels of physical fitness [exercise capacity] in relation to survival, mortality or nonfatal cardiovascular events. The studies had at least 50 participants, and had a follow-up period of at least 6 months. The databases searched are described in the introduction to the literature review [Chapter 3]. My search initially yielded 161 references dating back to 1953. The following sections review firstly observational, and secondly intervention studies, under the three sub-headings:

1. Baseline physical fitness and mortality
2. Baseline physical fitness and risk of nonfatal cardiovascular events
3. Changes in levels of physical fitness or exercise capacity and risk of mortality and nonfatal cardiovascular events.

#### ***4.5 Observational studies***

Seven observational studies focus on the prognostic effect of cardiorespiratory fitness on survival in people with established coronary heart disease (Awad-Elkarim et al 2003; Fioretti et al 1988; Froelicher 1994; Kavanagh et al 2002; Kavanagh et al 2003; Vanhees et al 1995; Vanhees et al 1994). Details of these studies are shown in Tables 4:1a and 4:1b. Five of the studies report on the relationship between baseline fitness and survival, and two report the effect of changes in exercise capacity on mortality in coronary heart disease.

Table 4:1a Eligible observational studies that have incorporated measures of cardiorespiratory fitness and mortality or cardiovascular events as main outcomes

Authors, year, country	Study objective	Participants			Fitness Test		Main outcomes evaluated	Period of follow up
		Eligible	% Female	Mean Age	Type	Measures	Timing	
Fioretti et al 1988 The Netherlands	Exercise capacity predictive of 1 year mortality	327 post MI	8	51±10	Symptom limited bicycle. With 10 or 20[w] increments each minute	Watts [w]	Pre-discharge & 12 weeks	Prognostic exercise capacity post CR All-cause mortality Cardiac mortality
1 year								
Froelicher et al 1994 USA	Prognostic value of early exercise testing post MI	258 post MI	15	56 ±8	Low level treadmill. Up to 4 METS max with 4 x 3 minute stages up to 1.7mph	METS	Pre-discharge & 12 weeks	Baseline exercise capacity Cardiovascular [CV] mortality
10.6 years								
Vanhees et al 1994 Belgium	Prognostic value of baseline peak exercise capacity.	527 post MI & post CABG attending CR	0	53±8	Maximal bicycle test with expired gas analysis. 20w increased by 30w every 3-4 minutes	VO <sub>2peak</sub>	10-15 weeks post event maximal exercise test	Baseline exercise capacity All-cause mortality CV mortality
11.8 years								
Vanhees et al 1995 Belgium	Prognostic value of training induced peak exercise capacity	417 post MI & post CABG attending CR	0	53±8	Maximal bicycle test with expired gas analysis. 20w increased by 30w every 3-4 minutes	VO <sub>2peak</sub>	10-15 weeks post event maximal exercise test	Change in exercise capacity after CR All-cause mortality CV mortality
11.8 years								
Kavanagh et al 2002 Canada	Prediction of long term prognosis after CR in males	12,169 with coronary heart disease, [CHD] attending CR	0	55±9	Symptom limited bicycle with expired gas analysis test	VO <sub>2peak</sub>	9-18 weeks post event or referral	Baseline exercise capacity All-cause mortality CV mortality
median 7.9 years								

Authors, year, country	Study objective	Participants		Fitness Test		Main outcomes evaluated	Period of follow up
		Eligible	% Female	Mean Age	Type	Measures	Timing
Kavanagh et al 2003 Canada	Prediction of long term prognosis after CR in females	2,380 with CHD, attending CR	100	59±10	Symptom limited bicycle with expired gas analysis test	VO <sub>2peak</sub>	9-18 weeks post event or referral
						Baseline exercise capacity	median 4.5 years
						All-cause mortality	
						CV mortality	
Awad-Elkarim et al 2003 UK	Prognostic value of exercise testing in young MI survivors	255 post MI	18	48	Maximal treadmill using the modified Bruce protocol	Duration of time on treadmill	6 weeks post MI
						<15 minutes or ≥15 minutes	Baseline exercise duration
							CV events
							15 years

Table 4:1b Results from eligible observational studies

Authors, year, country	Study objective	Study results	Comments
Fioretti et al 1988 The Netherlands	Long term survival and social fate post MI	Baseline exercise capacity predicted mortality 34 completers had 100% exercise capacity when compared with ‘normals’ – same age, height, gender and no heart disease	Drop out rate 25%
		Exercise capacity rose by 26 % (p<0.001) between start and end of CR	
Froelicher et al 1994 USA	Prognostic value of early exercise testing post MI	Exercise capacity was not predictive of CV death and was excluded from other models HR 1.6 CI 1.0, 6.5.	Drop out rate 5%
Vanhees et al 1994 Belgium	Prognostic value of baseline peak exercise capacity	33/53 CV deaths. An increase of VO <sub>2peak</sub> by 1 litre/min gave a decrease in all-cause (57%) and CV mortality (71%) HR 0.43 and 0.289.	



Authors, year, country	Study objective	Study results	Comments
Vanhees et al 1995 Belgium	Prognostic value of training induced peak exercise capacity	<p>All-cause mortality 8.9%. 21/37 CV deaths.</p> <p>Change in <math>VO_{2peak}</math> at end of exercise training predicted CV mortality HR 0.20. An extra increase by 1% in exercise capacity gave a decrease of 2% in CV mortality.</p> <p>Change in <math>VO_{2peak}</math> at end of exercise training did not predict all-cause mortality</p> <p>When the regression model was adjusted for <math>VO_{2peak}</math> before CR exercise training, <math>VO_{peak}</math> after CR remained a significant independent predictor for all-cause and CV mortality.</p>	<p>Drop out rate 17.6% from CR with additional 3.9% not completing second exercise test</p> <p>One patient lost to long term follow up</p>
Kavanagh et al 2002 Canada	Prediction of long term prognosis after CR in males	<p><math>VO_{2peak}</math> rose by 33% (<math>p&lt;0.001</math>) between start of and end of CR</p> <p><math>VO_{2peak}</math> predicted all-cause and cardiac mortality.</p> <p>All-cause mortality HR 1.00 [reference was low fitness level], compared to 0.66 [moderate fitness] &amp; 0.45 [high fitness].</p> <p>Cardiac mortality HR 1.00[reference was low fitness level], 0.62[moderate fitness], &amp; 0.39 [high fitness]</p> <p>For every 1ml/kg/min rise in initial <math>VO_{2peak}</math> there was an associated 9% lower cardiac mortality.</p>	Drop out rate 4.8%
Kavanagh et al 2003 Canada	Prediction of long term prognosis after CR in females	<p><math>VO_{2peak}</math> was a powerful predictor of cardiac mortality [reference was low fitness compared to high fitness] HR 0.5, (<math>p&lt;0.001</math>).</p> <p>For every 1ml/kg/min rise in initial <math>VO_{2peak}</math> there was an associated 10% lower cardiac mortality.</p>	Drop out rate 4.3%
Awad-Elkarim et al 2003 UK	Prognostic value of exercise testing in young MI survivors	<p>Exercise duration of either <math>\geq 15</math>min or <math>&lt; 15</math>min on treadmill predicted time to first CV event, HR 0.56, CI 0.38,0.82 (<math>p = 0.003</math>).</p> <p>Odds ratio for event free survival for the fitter participants was 0.35, CI 0.13,0.98 (<math>p = 0.05</math>).</p>	Drop out rate 13%

#### **4.5.1 Baseline physical fitness and mortality**

The largest cohort study of CR patients followed 12,169 white professional or managerial males, in their mid-fifties, who had attended a Canadian CR programme and were followed up for between 4 to 29 years with a median follow up time of 7.9 years as seen in Tables 4:1a and 4:1b (Kavanagh et al 2002). Initially 13,131 men were recruited to CR, of whom 154 were excluded from the study if they were unable to participate in exercise testing which used expired gas analysis, or if they did not have coronary heart disease. The remaining patients performed a maximal exercise test, unless contra-indicated, on a cycle ergometer at the start of CR to determine a baseline level of physical fitness. Repeat exercise testing was carried out  $13.4 \pm 3.9$  weeks after enrolment. Over half the patients had suffered a myocardial infarction, a quarter had undergone bypass surgery and the remainder had non-specific diagnoses of coronary heart disease. Patient data on coronary risk factors such as smoking habit, blood pressure and fitness levels at entry to CR were examined for their association with cardiac and all-cause mortality and to look for possible predictors of survival. Baseline fitness was treated firstly as a continuous variable and also categorised into three levels of fitness: low [ $\text{VO}_{2\text{peak}} < 15 \text{ ml/kg/min}$ ], moderate [ $\text{VO}_{2\text{peak}} 15\text{-}22 \text{ ml/kg/min}$ ] and high [ $\text{VO}_{2\text{peak}} > 22 \text{ ml/kg/min}$ ]. The data were analysed using a Cox proportional hazards model.

During the follow up period, 19.3% of the cohort died. Almost half of the deaths were from cardiovascular causes. This study showed baseline fitness [VO<sub>2peak</sub>] to be a powerful predictor of both all-cause and cardiac mortality for participants as seen in Table 4:2. The high fitness category was associated with a 55% reduction in the risk of death from all causes and a 61% reduction in the risk of cardiac mortality. The moderate fitness category was associated with a 34% reduction in the risk of death from all causes and a 38% reduction in the risk of cardiac mortality. An important finding from this study was the association of a 9% reduction in cardiac mortality [HR 0.91], for every one ml/kg/min increment of the initial peak oxygen intake. Being on digoxin medication for a cardiac rhythm disturbance (p<0.0001), or a current smoker (p<0.0001), or having a diagnosis of diabetes (p<0.0001) were also predictive of a higher risk of cardiac mortality.

**Table 4:2 Predictors of mortality in males attending CR**  
(Kavanagh et al 2002)

	High fitness	Moderate fitness	Low fitness	p value
All cause deaths	HR 0.45 CI 0.42,0.55	HR 0.66 CI 0.59,0.73	HR 1.00	<0.0001
Cardiac deaths	HR 0.39 CI 0.33,0.47	HR 0.62 CI 0.54,0.71	HR 1.00	<0.0001

The researchers also followed up 2,380 females from the same cohort. The females were aged 59.7 ±9.5 years (Kavanagh et al 2003). Half the participants were enrolled into the study following myocardial infarction, nearly a quarter had undergone coronary artery bypass procedures and the



remainder had other forms of coronary heart disease. Baseline fitness was measured in the same way. The baseline fitness levels were treated as a continuous variable and also as a binary variable, with the cut off point being VO<sub>2</sub> of 13ml/kg per minute, which equates to a little less than 4 METS. Data were analysed using a Cox proportional hazards model.

At the end of the follow-up period 12.8% of the cohort had died, of which just under half had died from cardiac causes. Treating baseline fitness as a binary variable, all-cause mortality was reduced by 29% and cardiac mortality was reduced by 50% for those with a VO<sub>2peak</sub> ≥13ml/kg/min [Table 4:3]. The female participants had a 1% lower level of cardiac mortality, compared to the males, [HR 0.90, 95% CI 0.85,0.96 (p=0.001)], for every 1 ml/kg/min increment in initial VO<sub>2peak</sub>. Being on digoxin (p=0.005), anti-arrhythmic therapy (p=0.0001) or having a diagnosis of diabetes (p=0.0001) was predictive of a higher risk of cardiac mortality.

**Table 4:3 Predictors of mortality in females attending CR**  
(Kavanagh et al 2003)

	High fitness	Low fitness	p value
All cause deaths	HR 0.71 CI 0.53,0.95	HR 1.00	0.0204
Cardiac deaths	HR 0.5 CI 0.34,0.76	HR 1.00	0.001

There are several interesting points concerning the two studies I have described above. Firstly, the baseline measures of fitness were recorded at 13.4 ±3.9 weeks post cardiac event, which is later than often reported in CR

studies (Bethell and Mullee 1990; Carson et al 1982; Dugmore et al 1999). In a randomised controlled trial (Bethell and Mullee 1990) participants performed exit CR exercise tests at 18 weeks post infarction, which was the time that some of Kavanagh's participants were undergoing their pre-CR exercise testing. Following myocardial infarction there is tendency towards spontaneous recovery with improvement in cardiorespiratory function during the first 3 weeks to 6 months post infarction (DeBusk 1977; Franklin et al 1992; Greenland and Chu 1988; Haskell and DeBusk 1979). Therefore the sooner after infarction that exercise capacity is measured the lower it may be. Baseline fitness reported for considerably younger male myocardial infarction participants who underwent exercise testing post infarct was 23.6ml/kg/min (Vanhees et al 1995), whereas Kavanagh's male myocardial infarction participants had a mean baseline  $\text{VO}_2$  of 20.5ml/kg/min when assessment was several weeks later.

One limitation of this research is that co-morbidity, complex pathology and psychological state were not accounted for with the exception of diabetes. Secondly, in addition, the researchers did not explain why some patients were unable to perform the exercise tests, although one reason for this may have been due to co-morbid illness that limits their ability to participate. It is also not clear why the female patients were described as having uncomplicated stable coronary disease even though diagnoses were similar to those assigned to the male patients. Because the risk of mortality in stable coronary heart disease is lower than the risk after acute myocardial infarction

or acute coronary syndrome, the outcome for the female cohort may only be generalisable to individual women with stable coronary heart disease. Finally, the reporting period for both studies spans 30 years, from 1968 – 1998. During these 30 years treatments changed and survival after a cardiac event improved.

Other researchers have also examined the importance of baseline fitness levels. Froelicher and colleagues looked at treadmill exercise testing variables as predictors of cardiovascular mortality in a group of 258 patients [39 females], under 70 years, who were admitted to hospital following an acute myocardial infarction between 1977 and 1980 (Froelicher 1994). Low-level exercise treadmill tests were performed on participants with uncomplicated pathology before discharge from hospital following the index cardiac event. The participants were followed up for 10.6 years at which point 27.5 % of the cohort had died, the majority [21.7%] from cardiovascular causes. The drop out rate from the study was low at 5%. The researchers reported that ST segment elevation, or ST depression on an ECG, and a hypotensive blood pressure response to the exercise testing were predictive of cardiovascular death. However, in this small group of participants baseline fitness was not predictive of cardiovascular death [HR 1.6, 95% CI 1.0,6.5] and was subsequently excluded from further analyses.



#### **4.5.2 Baseline physical fitness, mortality and risk of nonfatal cardiovascular events**

A study has been published recently which examined the prognostic value of early exercise testing and coronary angiography in young survivors of a myocardial infarction (Awad-Elkarim et al 2003). From 255 eligible patients, 150, including 20 females, were recruited to undergo early exercise testing and angiography. Physical fitness was measured and expressed by the amount of time endured on treadmill exercise testing, and the participants were divided into 2 groups: those who could achieve more than 15 minutes of the modified Bruce protocol, which equates to 9 minutes of the full Bruce protocol, and those who could not manage 15 minutes of the modified protocol. The participants were followed up for 15 years. As well as reporting on survival, the study also reported the incidence of nonfatal events. During the follow up period there were 44 deaths. One hundred percent of the 121 female participants had suffered at least one more cardiovascular event. Those who had been able to complete 15 minutes of the exercise protocol at the baseline exercise assessment were less likely to suffer a recurrent cardiovascular event than those who were unable to do so. The hazard ratio for the predicted risk for the participants who were able to achieve a treadmill test of 15 minutes or more was 0.56 [CI 0.38,0.82 ( $p=0.003$ )]. The event free survival odds ratio was 0.35 [CI 0.13,0.98 ( $p=0.05$ )].

This study showed the importance of baseline fitness on survival for comparatively young participants from the infarct population. However, the number of patients recruited to the study was small, the reported drop out rate was 13%, and there were few female participants in the cohort. The effect of fitness on other manifestations of coronary heart disease remains unclear.

#### **4.5.3 Changes in levels of physical fitness and risk of mortality and nonfatal cardiovascular events**

For coronary patients who have had a recent myocardial infarction, the  $VO_{2max}$  is 10-30% lower than matched controls without overt coronary heart disease (Bruce et al 1974; Sanne 1978). Two observational studies have measured change in fitness levels in association with mortality and morbidity outcome measures. These studies examined baseline measures and also changes in measures of fitness following exercise training as predictors of survival (Fioretti et al 1988; Vanhees et al 1995).

The first study followed a group of low risk male patients, with an age range of 24 to 74 years, referred to a CR programme of 3 month's duration following myocardial infarction or coronary artery bypass grafting or both, between 1978 and 1988 (Vanhees et al 1995). Some of the patients were part of the same cohort which the authors had previously described (Vanhees et al 1994). Patients were followed up for an average of 6.2 years. The drop out rate from the CR component was 17.6% and a further 3.9% of participants failed to complete the second exercise test at the end of CR.



The remaining 417 patients underwent cycle ergometry exercise testing to the point of exhaustion with respiratory gas analysis at the start and end of CR. The mean age of the group was 53 years and the co-morbidity accounted for included diabetes [3%] and chest pain [24%]. The mean body mass index of the patients was 24.8 and the mean  $\text{VO}_2$  before starting CR was 23.6ml/kg/min.

During the CR programme the patients accumulated just under 4 hours of exercise training per week. Exercise capacity was expressed as  $\text{VO}_{2\text{peak}}$ . The improvement in measured  $\text{VO}_2$  following completion of the CR programme was significant ( $p<0.001$ ) with the mean  $\text{VO}_2$  rising to 30.8ml/kg/min. One patient was lost to follow-up, and therefore survival analyses were reported on 416 patients. Single and multiple Cox proportional hazards regression models were fitted to calculate the relative hazard rate for deaths from cardiovascular and all causes.

Nearly 9% of participants died during the 10-year follow-up period, of which just over half the deaths were attributable to cardiovascular causes. The mean increase in  $\text{VO}_{2\text{peak}}$  by the end of the CR course was reported as 33%. Resting heart rates and heart rates during sub-maximal exercise were also lower by the end of the exercise programme indicating improved cardiovascular status. The hazard rates for  $\text{VO}_{2\text{peak}}$  before and after CR and the change in  $\text{VO}_{2\text{peak}}$  were put into a regression model unadjusted and also adjusted for age, current smoking, diabetes and hypertension.  $\text{VO}_{2\text{peak}}$



recorded at the end of CR was a better predictor of survival than the baseline measures. The relative hazard ratio for the percentage increase in  $\text{VO}_{2\text{peak}}$  between the start and end of CR was 0.98 ( $p < 0.05$ ). This showed that a 1% rise in  $\text{VO}_{2\text{peak}}$  at the end of CR was associated with a decrease in cardiovascular mortality of 2%.

The results from this study were limited by several factors. The researchers were not able to account for the patients who were not referred to CR, nor for those who refused to attend following invitation. The cohort consisted of patients who opted into the CR programme. The reported drop out rate was 17.6%. In addition the authors did not report any co-morbid conditions other than diabetes, which suggests that the patients did not have any concomitant orthopaedic or musculo-skeletal conditions, often prevalent in non-selected CR cohorts. An increase in  $\text{VO}_{2\text{peak}}$  of 33% is uncommon in coronary patients who have undergone a short course of CR exercise training, although the frequency and dose of weekly supervised exercise at four sessions weekly was greater than often reported from CR programmes, where one or two sessions are the custom. For instance in a study performed in the United Kingdom  $\text{VO}_{2\text{peak}}$  measured by expired gas analysis increased between 13-15% following an 8 month period of exercise (Dugmore et al 1999). Finally, the mean body mass index of the cohort was lower than is usually reported in male patients who attend CR programmes. The median body mass index of the patients in the cohort that is the subject of this thesis was much higher at  $27.2\text{kg/m}^2$  (22.0,35.1) for the females and

26.8kg/m<sup>2</sup> (22.9,32.7) for the males. The participants enrolled in Vanhees' study were atypical representatives of people with coronary disease.

One other small observational study reports on changes in physical fitness and mortality after attendance at CR (Fioretti et al 1988). The study aimed to establish whether haemodynamic<sup>ii</sup> measurements such as nuclear ventriculography<sup>iii</sup> ejection fraction<sup>iv</sup> and exercise capacity assessed during the acute phase of myocardial infarction were predictive of exercise capacity at the end of CR and also 1-year mortality. Under half of the patients admitted to a coronary care unit [CCU] with a diagnosis of a myocardial infarction were selected to undergo haemodynamic investigations as seen in Figure 4:1.

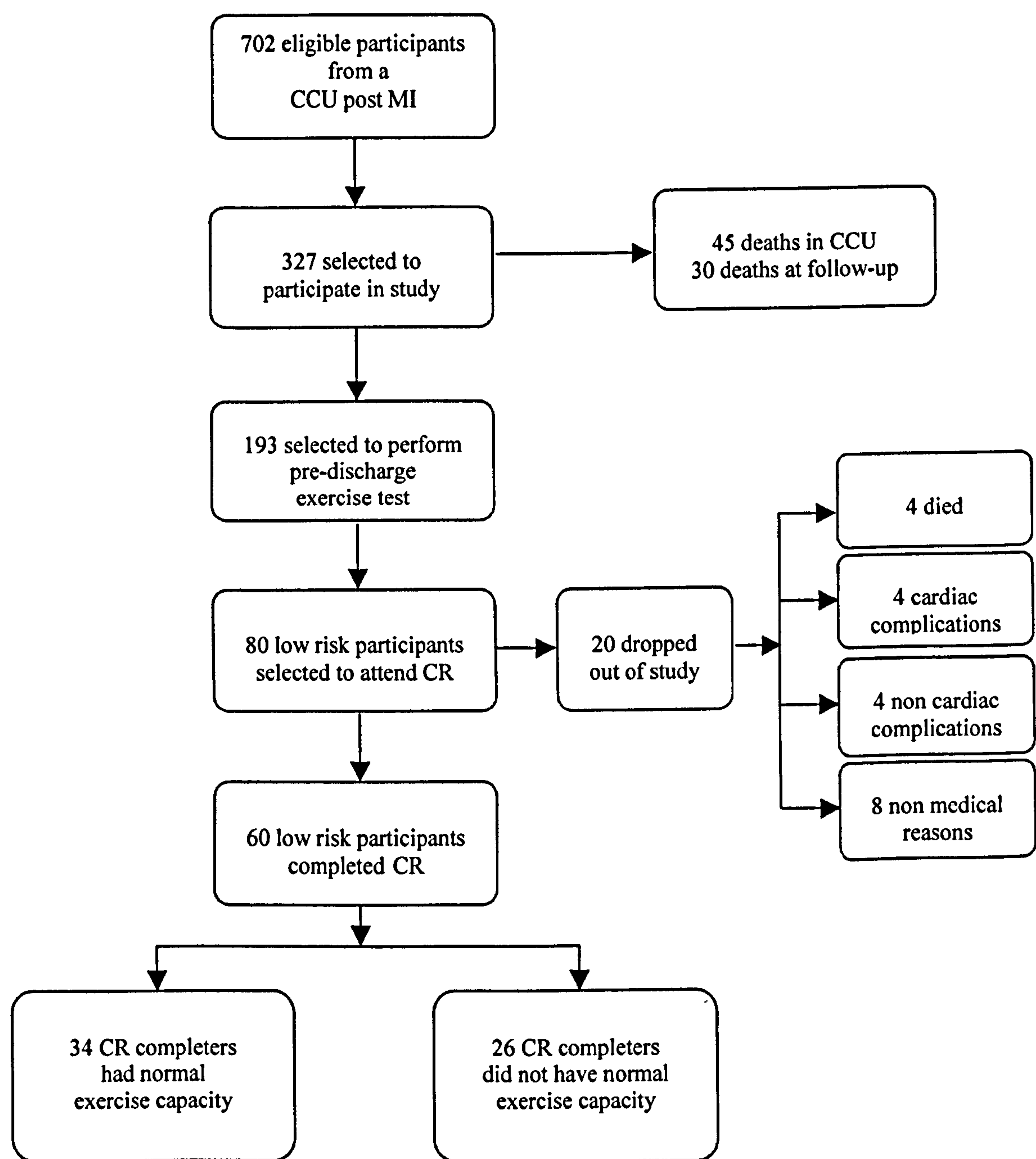
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<sup>ii</sup> Haemodynamic refers to the dynamic regulation of blood flow

<sup>iii</sup> Nuclear ventriculography involves the use of radioactive tracers which show up the heart chambers and blood vessels

<sup>iv</sup> Ejection fraction is the amount of blood pumped out of the left ventricle as it contracts

**Figure 4:1 Flowchart illustrating study enrolment and outcome**  
(Fioretti et al 1988)



Only those with complicated infarctions or those taking part in a thrombolytic trial were recruited to the study initially. Of these 80 patients were recruited to a 3-month long CR programme with supervised exercise sessions lasting 1.5 hours twice a week and 200 patients were not offered CR. The drop out rate



following initial enrolment was 25%. Sixty participants completed a second exercise test at the end of CR. The participants were divided into 2 groups depending upon the outcome measure of exercise capacity at the end of CR. Those with a normal exercise capacity which was measured in watts [ie a capacity of 100% or more, as compared with a normal population of the same gender, age and height] formed one group, and those with less than normal capacity the other. Exercise capacity of those who had completed CR increased by 26% ( $p<0.001$ ) over the 3 months of supervised exercise training at CR. One year mortality was reported for 327 patients originally selected for the study, of whom 14% died during initial hospital admission and 9% died within the year. Baseline exercise capacity but not exercise capacity at the end of CR predicted survival for the 60 participants for whom a change in fitness result was obtained. This differed from Vanhees and colleagues' findings, which showed  $VO_{2peak}$  at the end of CR to be predictive of survival.

The results from this study are limited for several reasons. The sample size was small and predominantly [92%] male. Although the original cohort was composed of patients with complicated infarctions, those who attended the CR programme were a selected group of patients. They were younger [mean age of 51 years], had a greater mean ejection fraction ( $p=0.05$ ) and less sick Killip class ( $p=0.005$ ) than the patients who were not offered CR. Finally, the authors did not account for non-cardiac co-morbidity in the analyses.

## **4.6 *Intervention Studies***

### **4.6.1 Changes in levels of physical fitness and risk of mortality**

Fourteen intervention studies looked at changes in measures of physical fitness during exercise programmes and also assessed the risk of mortality. Most of these studies involve small numbers of male post myocardial infarction patients who have undergone CR. They report on measures of physical fitness, all-cause and cardiac mortality and the recurrence of nonfatal cardiovascular events. Results have often not reached statistical significance. It has been estimated that approximately 4,000 patients would be required to achieve significance in this type of research (Greenland and Chu 1988; Shephard 1985). The largest trial recruited 733 patients, of whom nearly half dropped out (Rechnitzer et al 1983). The main points from these studies are summarised in Tables 4:4a and 4:4b. The majority of intervention studies enrolled male patients who had suffered a myocardial infarction (Bethell 1987; Bethell et al 1999; Bethell and Mullee 1990; Carson et al 1982; Dorn et al 1999; Dugmore et al 1999; Hedback et al 1993; Kallio et al 1979; Marra et al 1985; Rechnitzer et al 1983; Roman et al 1983; Shaw 1981; Stern and Cleary 1982; Vermeulen et al 1983; Wilhelmsen et al 1975). Only two studies focus on patients who had undergone angioplasty (Belardinelli et al 2001; Hofman-Bang et al 1999). There were no studies on patients who had undergone coronary bypass graft operations.

The largest intervention study was performed by the National Exercise Heart Disease Project group of researchers (Dorn et al 1999; Shaw 1981; Stern and Cleary 1982) who have followed up a group of 651, young, low risk male post myocardial infarction patients for up to 19 years, after they were randomised to join either supervised exercise programmes or undergo usual care which consisted of follow up but without structured exercise. Fitness was measured in METS from treadmill exercise testing. The exercise capacity of the treatment group improved significantly over the period of the intervention which lasted for up to 3 years, and ranged from an 8-14% reduction [dependent on the timing of the outcome assessments] in all-cause mortality, for every single MET gained in fitness. The control group also showed an improvement in exercise capacity and for those who took up exercise, reduced mortality. Thirty-one percent of the control group had taken up exercise, which may have influenced outcomes. However, the reduction in mortality was not significantly different between the two groups and diminished over the time of the follow-up period.



Table 4:4a Eligible intervention studies that have incorporated measures of cardio-respiratory fitness and mortality or cardiovascular events as main outcome

Acronym, authors, year, country, study design	Participants			Fitness Test		Main outcomes evaluated	Key components		Period of follow up
	Eligible	% Female	Mean Age	Intervention Group	Control Group	Type	Measures	Timing	
Wilhelmsen et al 1975 Sweden RCT <sup>v</sup>	315 post MI	11	51	158	157	Bicycle	Max VO <sub>2</sub> uptake	12 weeks post MI & at 1 year	All-cause mortality Nonfatal re-infarction Exercise capacity
Kallio et al 1979 Finland RCT	375 post MI	20	54	188	187	Bicycle	Not stated	1, 2 & 3 years	All-cause mortality Cardiac mortality Nonfatal re-infarction Anginal symptoms Exercise capacity
The National Exercise Heart Disease Project Shaw 1981 Stern and Cleary 1982 Dorn et al United States of America 1999 Multi centred RCT	651 low risk post MI	0	52	315	319	Treadmill	METS in graded single stages	6, 12 & 24 months	All-cause mortality Cardiac mortality Nonfatal re-infarction Exercise capacity
Carson et al 1982 United Kingdom RCT	303 post MI	0	52	151	152	Symptom limited bicycle in 25w stages every 4 minutes starting at 50w	Watts [w]	6 weeks, 5 months, 1, 2 & 3 years	All-cause mortality Nonfatal re-infarction Exercise capacity

<sup>v</sup> RCT: Randomised controlled trial

Acronym, authors, year, country, study design	Participants				Fitness Test			Main outcomes evaluated	Key components		Period of follow up
	Eligible	% Female	Mean Age	Intervention Group	Control Group	Type	Measures		Timing	Description of Intervention	
Ontario Exercise Heart Collaborative Study Rechnitzer et al 1983 Canada Multi centred RCT	733 post MI	0	47.5	379	354	Symptom limited bicycle 1kg/min every minute increasing by same each minute	Kg/min	6 & 12 months, yearly	Fatal and nonfatal re-infarction Exercise capacity	High intensity exercise training Low intensity exercise training	4 years
Vermeulen et al 1983 The Netherlands RCT	98 post MI	0	49	47	51	Bicycle using expired gas analysis	VO <sub>2</sub>	4-6 weeks post MI	All-cause mortality Cardiac mortality Nonfatal re-infarction Change in NYHA™score	Comprehensive CR Usual care	5 years
Roman et al 1983 Chile Controlled trial	193 post MI	10	54	93	100	Bicycle using expired gas analysis	VO <sub>2</sub> max	3-6 months for intervention group 1 or 2 years for controls	All-cause mortality Cardiac mortality Nonfatal re-infarction Presence of angina Exercise capacity	Supervised exercise training No formal exercise training	9 years
Marra et al 1985 Italy RCT	167 post MI	?	50	84	83	Symptom limited bicycle 30w increments every 2 to 3 minutes	Watts	30-60 days post MI, yearly	All-cause mortality Cardiac mortality Nonfatal re-infarction Presence of angina Exercise capacity	Supervised exercise training in CR Unsupervised aerobic type of home exercise programme	4 years 7 months
PRECOR Group Saint et al 1991 France RCT	182 post MI	0	50	60 to CR 61 to counselling	61	Bicycle 20w every 2 minutes to max heart rate	Watts	2,12 & 24 months	All-cause mortality Nonfatal re-infarction Incidence of angina Exercise capacity	CR or counselling Usual care	2 years
Hedback et al Sweden 1993 Controlled trial	147 post MI	7	57	84	158	Bicycle	Watts	Not reported	All-cause mortality Cardiac mortality Nonfatal re-infarction Exercise capacity	Supervised exercise training in CR Usual care	10 years

<sup>vi</sup> NYHA: New York Heart Association

Acronym, authors, year, country, study design	Participants				Fitness Test		Main outcomes evaluated	Key components		Period of follow up		
	Eligible	% Female	Mean Age	Intervention Group	Control Group	Type		Measures	Timing		Description of Intervention	Management of Control Group
Bethell et al United Kingdom 1990 and 1999 RCT	200 post MI	0	54	99	101	Symptom limited bicycle	VO <sub>2peak</sub>	6 & 18 weeks	Cardiac mortality Nonfatal re-infarction Exercise capacity	Supervised exercise training in CR	Usual care	11 years
Hofman-Bang et al Sweden 1999 RCT	151 post PTCA <sup>vii</sup>	11	53	41	41	Bicycle	Watts	Post PTCA	Mortality Exercise capacity	Residential CR for 4 weeks + maintenance contact for 2 years	Usual care	2 years
Dugmore et al United Kingdom 1999 RCT	124 post MI	2	55	62	62	Symptom limited modified Bruce on Treadmill, with expired gas analysis	VO <sub>2</sub>	3 weeks post MI, 4, 8 & 12 months	Mortality Nonfatal re-infarction Exercise capacity	Supervised exercise training in CR	No formal exercise training	5 years
The ETICA Trial Belardinelli et al Italy & United States of America 2001 RCT	118 post PTCA	16	57	59	59	Bicycle with expired gas analysis	VO <sub>2</sub>	25 days post PTCA, 6 monthly	Nonfatal cardiac events Exercise capacity	Supervised exercise training in CR	Usual care	2 years 9 months

<sup>vii</sup> PTCA: Percutaneous transluminal coronary angioplasty



Table 4:4b Results from eligible intervention studies

Acronym, authors, year, country, study design	Study results	Comments
Wilhelmsen et al 1975 Sweden RCT	All-cause mortality: NS <sup>viii</sup> difference between groups Nonfatal re-infarction: NS difference between groups. Exercise capacity: VO <sub>2</sub> greater in intervention group (p<0.001)	Small sample 89% males Young population High drop out rate of 39% Baseline characteristics different between groups
Kallio et al 1979 Finland RCT	All-cause mortality: NS (p<0.10) between groups Cardiac mortality: reduced in intervention group (p= 0.02) Nonfatal re-infarction: NS (p<0.10) between groups (p<0.10) Recurrence of angina: NS between groups Exercise capacity: NS between groups.	Small sample 80% males Young population Distribution of deaths not clear Nonfatal re-infarction at end of year 1 not reported Method of randomisation not described Physical fitness outcomes not described
The National Exercise Heart Disease Project  Shaw 1981 Stern and Cleary 1982 Dorn et al United States of America 1999 Multi centred RCT	All-cause mortality: NS between groups Cardiac mortality: NS between groups Nonfatal re-infarction: NS between groups Exercise capacity: Each single MET gain in fitness was associated with 8% to 14% reduction in all- cause mortality. Exercise participants had a NS reduction in mortality risk early in the follow up period. Benefits diminished as time since participation increased. Improved exercise capacity resulted in survival benefits for the whole cohort over 19-year follow up period.	Small sample 100% males Young population 31% control group took up exercise 23% of intervention group had stopped exercising
Carson et al 1982 United Kingdom RCT	All-cause mortality: NS difference between groups Nonfatal re-infarction: NS difference between groups Exercise capacity: NS difference between groups	Small sample 100% males Young population Drop out rate of 21% Method of randomisation not described Cardiac mortality not reported

<sup>viii</sup> NS: Non significant

Acronym, authors, year, country, study design	Study results	Comments
Ontario Exercise Heart Collaborative Study Rechnitzer et al 1983 Canada Multi centred RCT	Fatal and nonfatal re-infarction: NS difference between groups Exercise capacity: High intensity group had greater reduction in heart rate at 4 years (p=0.001)	Small sample 100% males Young population High drop out rate of 45.4%
Vermeulen et al 1983 The Netherlands RCT	All-cause mortality: NS difference between 2 groups Cardiac mortality: NS difference between groups Nonfatal re-infarction: Higher evidence of progressive disease in controls (p<0.05) NYHA score: 10 controls versus 4 intervention group became NYHA 3-4	Small sample 100% males Young low risk population Drop out rate not reported Method of randomisation not described Baseline exercise capacity not reported, but these participants were from the same cohort as Wilhemsen et al recruited in 1975
Roman et al 1983 Chile Controlled trial	All-cause mortality: NS difference between 2 groups Cardiac mortality: NS difference between groups Nonfatal re-infarction: NS between groups (p<0.1>0.05) Angina: less frequent intervention group (p<0.005). Exercise capacity improved in intervention group no p values reported	Small sample 90% males Young population Method of randomisation not described Exercise capacity: No power calculations
Marra et al 1985 Italy RCT	All-cause mortality: NS between groups Cardiac mortality: NS between groups Nonfatal re-infarction: NS between groups Presence of angina: NS between groups Exercise capacity: improved in intervention group (p = 0.001) Maximum heart rate and double product (heart rate x systolic blood pressure) decreased in intervention group (p = 0.001)	Small sample Number of females not stated Low risk participants Drop outs 3.5% Method of randomisation not described Excluded 43% of 'eligible' participants after exercise test but before randomisation 8% of control group took up exercise
PRECOR Group Saint et al 1991 France RCT	All-cause mortality: Lower in intervention group (p=0.03) Nonfatal re-infarction: NS between all groups Incidence of angina: NS between all groups Exercise capacity: 50% of intervention group reached higher maximal heart rates (p=0.001)	Small sample 100% males Young population Low risk participants No drop outs Method of randomisation not specified
Hedback et al Sweden 1993 Controlled trial	At 5 years: All-cause mortality and cardiac mortality: NS between the groups. CV events: less in intervention group (p<0.05) At 10 years: All-cause mortality: less in intervention group (p<0.01) Cardiac mortality: less in intervention group (p<0.001) Nonfatal re-infarction: lower in intervention group (p<0.001) Exercise capacity at 1 year: mean increase in fitness from 91 watts to 131 watts for intervention group.	Small sample 92.5% males Selected sample as only 123 of original 147 patients were offered exercise training, of whom 39 declined and 6 dropped out (7%) at start of programme No power calculations reported for exercise capacity



Acronym, authors, year, country, study design	Study results	Comments
Bethell et al United Kingdom 1990 and 1999 RCT	Cardiac mortality: NS difference between groups Nonfatal re-infarction: reported as only via questionnaire responses (<100%) Exercise capacity: mean $\text{VO}_2$ had risen in intervention and control groups at second exercise test (18 weeks post event) compared with baseline ( $p<0.001$ ). Mean double product rose in intervention group ( $p<0.001$ ) post CR, but not in control group.	Small sample 100% males Method of randomisation not described Sicker patients excluded Total mortality not reported
Hofman-Bang et al Sweden 1999 RCT	Mortality: One death reported in <2 years follow up. Year 1: 37% of intervention group versus 32% of controls admitted to hospital. Year 2: 4% of intervention group versus 20% of controls admitted to hospital. Exercise capacity: increased in the intervention group ( $p<0.05$ )	Small sample Young population 89% males Short follow up period Selected group of employed and fitter patients who were able to achieve $\leq 70$ watts when undergoing fitness test before randomisation
Dugmore et al United Kingdom 1999 RCT	Mortality: NS differences between groups Nonfatal re-infarction: NS differences between groups Exercise capacity: Significant improvements in cardio-respiratory fitness ( $p<0.01-0.001$ )	Small sample size 98% males Method of randomisation not described
The ETICA Trial Belardinelli et al Italy & United States of America 2001 RCT	Nonfatal cardiac event: more frequent in controls ( $p = 0.0008$ ) Intervention group: lower admission to hospital. Exercise capacity: $\text{VO}_{2\text{peak}}$ increased by 26% in intervention group and correlated with improved Quality of Life measure ( $r = 0.78$ , $p<0.001$ ), but not type of percutaneous procedure performed. Exercise training predicted CV events ( $p = 0.008$ ).	Small sample 84% males No drop outs reported Method of randomisation not described Short follow up period



Another large multi-centred randomised controlled trial, the Ontario Exercise Collaborative Study, recruited 733 young males post myocardial infarction to exercise programmes (Rechnitzer et al 1983). The participants were randomised to either high or low intensity exercise groups and joined an exercise programme between 2 to 12 months after their index cardiac event. The exercise intervention lasted for 4 years, which was the duration of the follow up period. Four hundred participants completed the study. Results from this study showed that the participants who had undergone high intensity exercise training had lower resting heart rates at the end of the study period ( $p=0.001$ ). In spite of this reduction in resting heart rate for the intensively trained exercisers and, in common with most of the other intervention studies, the researchers found that the difference between the high and low intensity exercise groups for fatal or nonfatal re-infarction was not significant. The results from this study are limited by its small sample size, the high drop out rate of 45% and its focus on young male participants whose mean age was 47.5 years.

The earliest study I found (Wilhelmsen et al 1975) randomised 315 participants to comprehensive CR or usual care. Fitness was measured by bicycle testing at 12 weeks post myocardial infarction and one year later. The participants were followed up over a 4-year period. There was no difference in either all-cause mortality or the incidence of nonfatal re-infarction between the 2 groups, although the intervention group had higher fitness levels at the end of CR ( $p<0.001$ ). However, the results from this study are limited by the small sample

size, high drop out rate of 39%, and preponderance of males in the cohort [89%]. In addition, although the participants had been randomised to either group via a random letter table system, there were several differences between the baseline characteristics of the two groups. For example the control group had higher levels of leisure and work-time physical activity pre-infarct, contained a larger percentage of hypertensive participants, and more of the controls were being treated with digoxin.

Between 1973 and 1978 Kallio (Kallio et al 1979) conducted a similar study, in Finland, on 375 participants post myocardial infarction, who were followed up for 3 years. The method of randomisation was not described. Change in exercise capacity at the start and end of CR was measured on a bicycle ergometer and long term follow-up considered all-cause and cardiac mortality, nonfatal re-infarction and the reoccurrence of angina as outcome measures. At the end of the study the researchers reported that there was no difference between the intervention and control groups for the incidence of nonfatal re-infarction, the recurrence of anginal symptoms or changes in exercise capacity. However, this study showed a significant reduction in cardiac mortality for the intervention group at the end of the 3-year follow-up period, 18.6% for the intervention group and 29.4% for the control group ( $p=0.02$ ). This study had two main limitations, the distribution of deaths was not clearly reported and also the number of nonfatal re-infarctions at the end of the first year of follow-up was not stated.



Carson (Carson et al 1982) performed the first randomised controlled trial of CR in the United Kingdom in the early eighties. They enrolled 303 male myocardial infarction participants to either supervised exercise training or usual care. Symptom limited baseline fitness was measured on a bicycle ergometer at 5 months post event and then yearly for up to 3 years. Outcomes measures included all-cause, but not cardiac, mortality, nonfatal re-infarction, and changes in exercise capacity. There were no differences in mortality reported between the 2 groups at the end of the study period. However, as in other studies, the sample involved only a small number of patients, and was further limited by its recruitment of young male participants post myocardial infarction and an overall drop out rate of 21%. The method of randomisation was not described.

A small study by Vermeulen (Vermeulen et al 1983) recruited 98 males post myocardial infarction to either comprehensive CR or usual care. The mean age of the study participants was 49 years. The follow-up period was 5 years. The exercise capacity of the participants was measured at 4-6 weeks after the index event using expired gas analysis and a bicycle ergometer. However, at the end of the follow-up period, the only difference between the 2 groups was a higher evidence of progressive disease in the controls than in the intervention group ( $p<0.05$ ).

In the same year Roman (Roman et al 1983) reported a small controlled trial to study survival and the recurrence of coronary events, over a 9 year period, in a group of patients who had recently suffered an acute myocardial



infarction. One hundred and ninety three patients were entered into the study. There were 93 patients in the intervention group who underwent exercise-based CR. One hundred 100 patients were matched for characteristics that might affect outcomes and became the control group and did not participate in CR. Baseline fitness was assessed by cycle ergometry using expired gas analysis to measure  $VO_{2max}$ .

The researchers reported no differences between the 2 groups over the study period, with the exception of the recurrence of anginal symptoms. There were fewer symptoms of angina per year in the CR group [5.1%] versus the controls [10.2%] ( $p < 0.005$ ). Exercise capacity was stated to have improved in the CR group, although no p values were reported. The results from this study are also limited by its small sample size and by the fact that the mainly male participants were not randomised into intervention or control groups.

Similar results were reported from Marra's research, which was published 2 years later. One hundred and sixty-seven patients diagnosed with an acute myocardial infarction, were selected as eligible for this study (Marra et al 1985). The study participants were randomised into an intervention group who underwent exercise training and a control group who were permitted to carry out unsupervised spontaneous aerobic type activities at home. All participants were exercise tested on a bicycle ergometer between 30-60 days post infarction and then annually thereafter for 4.7 years. Although there

were no differences between the groups in terms of mortality or nonfatal re-infarction rates, at the end of the supervised exercise training programme, the intervention group showed a significant improvement in exercise capacity ( $p<0.001$ ) and also a significantly decreased double product<sup>ix</sup> which reflects myocardial oxygen consumption at a given work load ( $p<0.001$ ). There are several limitations to this study. For example, 43% of initially eligible patients were excluded from the study after their first exercise test, as randomisation only took place post exercise testing. The number of females in the study was not stated, and the method of randomisation was not described. In addition, 8% of the control group became regular exercisers. All these factors may have affected the overall results reported in this study.

The PRECOR group (Precor 1991) of researchers from France studied the short and long term benefits of CR on fitness and survival in a group of 182 young male myocardial infarction survivors who were randomised to receive either CR or counselling as an intervention compared with a control group who were given usual care. The method of randomisation was not described. Baseline fitness level was established from a bicycle test and outcome measures obtained at 2, 12 and 24 months respectively. All participants were followed up for 2 years. Exercise tolerance was greater in the CR group at 2 months, compared with the counselling group, or those that had received usual care ( $p<10^{-8}$ ). Although re-infarction rates were similar across all 3 groups, all-cause mortality was found to be less in the CR

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<sup>ix</sup> The double product is the heart rate x systolic blood pressure divided by 100



group ( $p=0.03$ ) compared to the combined counselling and usual care groups. This study reinforces the beneficial effect of exercise training in CR for young, low risk male myocardial infarction patients when compared with counselling or usual care.

Hedback (Hedback et al 1993) reported similar results from an unrandomised controlled study. They recruited a selected sample of 123 participants post myocardial infarction to a CR exercise programme lasting 3 months and compared them with a group of controls from a neighbouring hospital. The participants were mostly males [7% females], and were followed up for 10 years. Although after 5 years there was no difference seen between the intervention and control groups, at the end of the follow-up period all-cause mortality ( $p<0.01$ ) and cardiac mortality ( $p<0.001$ ) were both less in the intervention group. Mean exercise capacity in the intervention group rose from 91 watts to 131 watts at a year post event. This study is also limited because the participants were not randomised to treatment or control groups.

Following on from Carson's study, which had been published in the early eighties, two more studies were performed during the nineties in the United Kingdom, which showed the benefits accrued by attendees of CR exercise programmes. Bethell and Mullee (Bethell and Mullee 1990) randomised 200 male patients under 65 years of age, who were diagnosed with an acute Q wave myocardial infarction using the WHO criteria to receive either CR or usual care. Baseline fitness levels were estimated from bicycle exercise tests at 6



weeks post event at the start of CR and repeated after 3 months of CR. Significant improvements in exercise capacity were seen for the intervention group ( $p<0.001$ ) at the end of CR training, although the researchers were unable to show a significant difference between intervention and control groups for either cardiac mortality or rates of nonfatal re-infarction when the cohort was followed up over the following 11 years (Bethell et al 1999). All-cause mortality was not reported in this study. There were two factors that may have affected the outcomes of this study. Firstly, some of the control group members became regular exercisers over the timeframe of the study. Secondly, the reported numbers of nonfatal re-infarctions may not be truly representative, as these were collected via self-reported questionnaires rather than through medical channels or the national register of deaths.

Dugmore and colleagues performed the third British study, matching 124 myocardial infarction patients of which 2 were female, for the site and severity of myocardial infarction (Dugmore et al 1999). All patients had been exercise tested using the modified Bruce protocol and expired gas analysis at 3 weeks post infarction and were then randomly allocated to join a supervised CR programme three times a week for 12 months, or to usual care, which excluded formal exercise training. Participants were then allocated into either a good prognosis group, which started exercise-based CR at 3 weeks post infarct or a poor prognosis group, which started CR at 8 weeks. Group allocation was dependent on the severity of the initiating event. Outcome measures included changes in fitness levels post CR, mortality and the recurrence of nonfatal re-

infarctions. The participants were exercise tested 3 times during the first year. Subsequent exercise tests were maximal assessments, and participants were followed up by questionnaires for 5 years.

Results were reported on the good and poor prognosis groups and the control group. At the end of the first year there were significant differences shown in levels of fitness for both good and poor prognosis groups who had increased  $VO_{2peak}$  by 13 to 15% compared to the control group. One of the criteria for being in the poor prognosis group had been an inability to complete 9 minutes of the modified Bruce protocol at the start of this study. The researchers reported 5 deaths due to re-infarctions during the 5 years of follow up, of which 2 were in the intervention group. Although there were no differences in mortality between the groups the intervention group fared better. They suffered fewer nonfatal re-infarctions 8% versus 22% ( $p < 0.05$ -0.01) and reported fewer anginal symptoms ( $p < 0.001$ ). This study reinforces the benefits accrued through increasing levels of physical fitness. However, it is limited by its focus on small numbers of predominantly male patients who had suffered a myocardial infarction.

#### **4.6.2 Changes in levels of physical fitness and risk of nonfatal cardiovascular events**

Most of the intervention studies I have discussed have reported the incidence of nonfatal re-infarction between groups, although they did not necessarily look at the recurrence of cardiovascular events, such as the incidence of cerebrovascular accident [stroke], as an outcome measure. Several of the

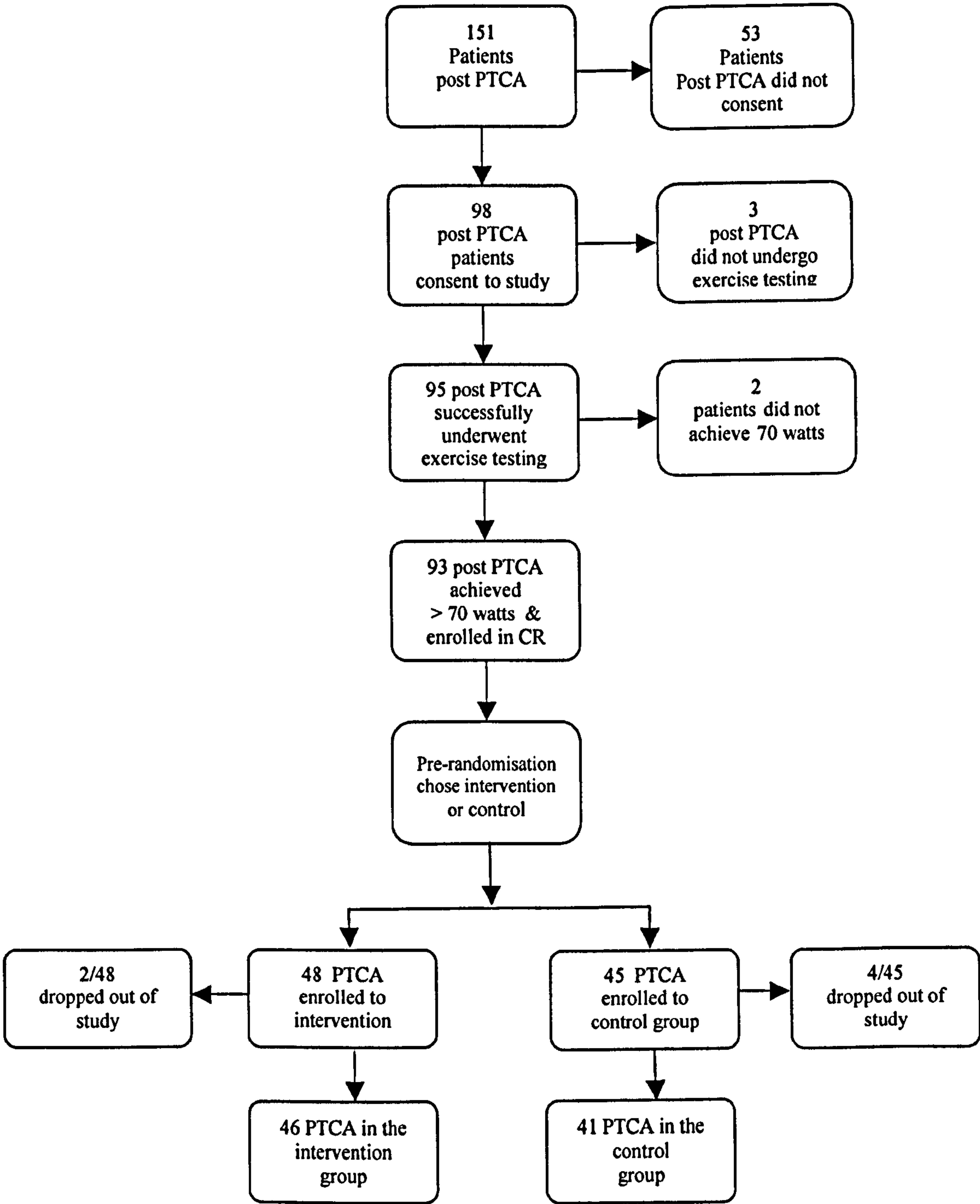


earlier studies report on lower, but non-significantly different rates of nonfatal events for the intervention groups (Dugmore et al 1999; Hedback et al 1993; Vermeulen et al 1983), whilst others have shown no difference between groups for this outcome (Bethell and Mullee 1990; Bethell et al 1999; Marra et al 1985; Precor 1991; Rechnitzer et al 1983; Roman et al 1983).

I found two studies on patients who have undergone angioplasty procedures that showed improvements in exercise capacity for the intervention groups. The duration of follow-up in both studies was less than 3 years. In the first study [Figure: 4.2], (Hofman-Bang et al 1999) a selected group of 46 participants from an initial cohort of 151 patients, performed a bicycle test, and attended a 4-week residential course focusing on multifactorial lifestyle behaviour components. At the end of the 2-year study period exercise capacity was shown to have improved significantly in the intervention group ( $p<0.05$ ) and overall a smaller proportion of the intervention group had hospital admissions in the second year ( $p<0.05$ ). One control patient died. The main limitations with this study were its small sample size, and the method of allocation, which required the patients to choose between opting into the residential course in the intervention group or to becoming a control and receiving usual care.



**Figure 4:2 Flowchart illustrating study enrolment to angioplasty study (Hoffman-Bang 1999)**



The second study [The ETICA<sup>x</sup> trial (Belardinelli et al 2001)] also examined the effects of exercise training in patients who had undergone angioplasty. One hundred and thirty patients were enrolled in the study after they had undergone successful angioplasty and were randomised into 2 matched groups. Exclusion criteria were no concomitant co-morbidity, which included having a diagnosis of diabetes. Some patients received primary angioplasty without thrombolysis following myocardial infarction. None of the patients received lipid lowering therapy during the study, as one of the outcomes of the study was to assess the effects of exercise training on the lipid profile. Half of the participants were randomised to attend an exercise programme for 6 months, whereas the controls were advised to be physically active, but not to participate in formal exercise training. Exercise testing was carried out using cycle ergometry with expired gas analysis.  $VO_{2peak}$  was recorded from the average measurement reached during the last 15 seconds of exercise.

Results showed a significant difference between groups for the increase in fitness. Exercise capacity in the intervention group improved by 26% during the study period. Fitness in the intervention group rose from 18.6 to 23.7ml/kg/min compared with the control group whose fitness decreased from 20.5 to 19.4ml/kg/min. The control group also experienced a greater number of cardiovascular events and hospital admissions as seen below in Table 4:5.

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<sup>x</sup> ETICA – Exercise training intervention after coronary angioplasty

**Table 4:5 Outcomes between intervention and control groups**  
(Belardinelli et al 2001)

	Exercise group n = 59	Control group n = 59	p value
	Over 3 years	Over 3 years	
Cardiovascular events	7	19	0.0008
Re-stenosis rate	15 of 52	17 of 52	0.81
Hospital admissions	6	17	<0.001
Coronary heart disease progression	7.6%	25%	0.038

A selection of 52 patients from each group underwent further angiography. A significantly lower rate of coronary heart disease progression was seen in the exercise group compared with the controls. Because the researchers had controlled for the effects of treating other risk factors, such as raised cholesterol levels, which had not been controlled by statin therapy, an important finding was that exercise component independently predicted cardiovascular events ( $p=0.008$ ) and also coronary heart disease progression ( $p=0.0006$ ). The findings from this study showed that improvements in exercise capacity in angioplasty patients were associated with a reduction in cardiovascular events and fewer hospital admissions post procedures regardless of the rate of re-stenosis.

**4.7 Summary**

All the studies I have described have incorporated a measure of baseline fitness and used a variety of methods for determining exercise capacity. It is difficult to draw comparisons between these studies for the following reasons. The lengths of the exercise interventions varied between the trials and



ranged from 6 weeks of supervised exercise to approximately 4 years, although the average duration of supervised exercise was about 12 weeks. The timing of the exercise assessments also varied from programme to programme. In the earlier programmes it is noticeable that the dropout rates ranged from 21% to 45.4% or were not reported. Nonetheless, as would be expected, outcomes relating to exercise capacity in the majority of programmes, including the National Exercise Heart Disease Project, were shown to improve significantly in the trained groups when compared to the controls (Bethell 1987; Bethell and Mullee 1990; Dugmore et al 1999; Hedback et al 1993; Wilhelmsen et al 1975). This improvement in fitness has been said to be up to 20% more than that which can occur spontaneously (Bethell 1992; Greenland and Chu 1988; Lipkin 1991; Sleight 1992).

It is clearly evident from most of these studies focusing on younger, male, myocardial infarction patients that baseline fitness levels are associated with fatal and nonfatal cardiovascular events. The importance of peak exercise capacity as a predictor for mortality in patients with other manifestations of coronary heart disease has also been well established. Some of the later studies have included older patients who have survived an initial infarct, but this is not true for most of the earlier research. Moreover, the long term effects of fitness levels in people with coronary heart disease who have not had a myocardial infarction are still unknown, although some research shows that similar beneficial physiological effects can be produced in patients with coronary heart disease who undergo exercise training (Engblom et al 1993).

For example the recent results from the ETICA trial indicate the importance of increasing exercise capacity after undergoing angioplasty procedures and its association with fewer cardiovascular events. It would be interesting to collect survival data on these patients.

Vanhees' study is the only study I identified which has shown the predictive value of a change in fitness following exercise training on mortality. However, his cohort was atypical of the coronary heart disease population, being limited to young, relatively slender males, post myocardial infarction or after coronary bypass grafting.

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## **Chapter 5**

# **The epidemiology of coronary heart disease progression and depression**

### ***5.1 Introduction***

It is not clear how depressive symptoms or disorders contribute to the progression of coronary atheroma (Levin 2005; Strike and Steptoe 2002). Current evidence from epidemiological and clinical studies suggests a complex relationship exists between psychosocial factors and coronary heart disease. In recent years some researchers have reported that depression is an independent risk factor for exacerbating symptoms in those with established disease (Carney et al 1999; Frasure-Smith 1995; Frasure-Smith and Lesperance 2005). If this association is confirmed, the diagnosis and subsequent treatment of depression for those with pre-existing coronary heart disease could be of prognostic importance.

#### **5.1.1 What is depression?**

The definition of depression needs clarifying. There is a clear distinction between depressive symptoms, which affect most of us at some time during our lives, and depressive disorders, which occur less frequently. ICD-10, The World Health Organisation's current system for disease classification, uses a list of ten symptoms of depression to distinguish between the different types of depressive episodes.



### **5.1.2 Depressive episodes**

There is a cluster of symptoms common to all depressive episodes. These are depressed mood, loss of interest and enjoyment of one's normal activities (also known as anhedonia), and fatigue. Associated symptoms which are also common in depression include poor sleep, reduced ability to concentrate, memory impairment, low self-esteem and self-confidence, feelings of guilt and unworthiness, pessimism, evidence of self-harm or suicidal feelings, and loss of appetite with concomitant weight loss. The minimum duration of symptoms consistent with an ICD-10 diagnosis of depressive episode is two weeks. The number and intensity of symptoms present at the same time, and the extent of impairment in normal, social and occupational functioning indicate the severity of depressive episodes. The person experiencing a severe depressive episode is unlikely to be working or leading a normal social life, whereas someone with a mild depressive disorder should be able to carry out regular activities of daily living, albeit with limitations.

The natural history of depression is of a remitting and recurring condition. Recurrent depressive disorder is the term used to describe the recurrence of a depressive episode, classified in ICD-10 as F33, with recovery being defined as the remission of a depressive episode for eight consecutive weeks.

### **5.1.3 The diagnosis of depression**

The diagnosis of depressive episodes and disorders in a research setting is best reached through the use of structured diagnostic clinical interview (Blumenthal and Lett 2005). Depressive symptoms on the other hand are readily assessed using self-report questionnaires. Two of the most commonly used instruments for assessing depressive symptoms are the Beck Depression Inventory (BDI) and the Center for Epidemiological Studies – Depression scale (CES-D) (Sheps and Rozanski 2005). Issues surrounding the value of the different methods for establishing psychological state are discussed in Chapter 8 in section 8.3.2.

### **5.1.4 The prevalence of depression**

In the United Kingdom, the most recent data on the prevalence of depression based on the DSM IV<sup>i</sup> criteria comes from a telephone survey of 4,972 subjects who were interviewed during 1994. They were asked three series of questions which assessed whether they were feeling down or depressed, or had feelings of hopelessness, or anhedonia. From this survey the researchers found the prevalence of depressive disorders in the general population was 5% [95% CI 4.4,5.6] being lower at 4.2% for males, versus 5.9% for females ( $p < 0.01$ ) (Ohayon et al 1999) but higher than had previously reported at 2.2% for males, 4.9% for females (Bebbington et al 1991) and 1.7% for males, 2.5% for females (Lewis et al 1992). This

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<sup>i</sup> DSM IV is the fourth [1994] of the Diagnostic and Statistical Manual of Mental Disorders. It lists different categories of mental disorders.

compares with a European prevalence of depressive disorders of 7.9% (Lepine et al 1997). The European prevalence of depressive symptoms, such as feeling down or depressed, was 9.7%, with a greater proportion of females reporting symptoms than males [11.7% versus 7.5%].

The current figure for the worldwide prevalence of depression is 10.4% and it is predicted that by 2020 depression will become a leading cause of disability and impairment worldwide (WHO 2006) and second only to coronary heart disease in the western world (Murray and Lopez 1996). The implications of early detection of depression and appropriate treatment is therefore of social and economic importance. For example several studies have shown that depressed patients have significantly greater impairments than the non-depressed in terms of social functioning and well-being (Fredman et al 1988; Weissman et al 1978; Wells et al 1989) and the global economic burden of depression is much higher than in other common illnesses. In 1991 although the estimated direct costs of the treatment of depression in the United Kingdom was £417 million (Jones and Cockrum 2000) which at that time was similar to the cost of treating hypertension at £439 million, (DOH 1996) the indirect costs and burden of depression were considerably higher and estimated to be £2.97 billion (Jones and Cockrum 2000).



## ***5.2 Strategy for searching and selection of studies***

I first carried out a scoping literature search which yielded 853 publications on the subject of depression and cardiovascular diseases. After examining these papers I decided to limit the search strategy to publications that focused on the impact of depression on coronary heart disease progression, rather than the spectrum of cardiovascular diseases, since my thesis concerns outcomes for patients with a diagnosis of coronary heart disease. The timescale for this part of my literature review extends back to the late 1960s, although nearly all the relevant articles I found have been published over the last ten years and in particular since the turn of this century. The literature selected as suitable for inclusion in this part of my review is divided into three chapters. The next chapter examines the relationship of depression to the pathophysiology of coronary heart disease progression and the final chapter in my literature review focuses on the role of antidepressant therapy and psychosocial interventions in coronary heart disease progression. The rest of this chapter focuses on the temporal association between depression and coronary heart disease; and whether depression is an independent risk factor for, or a consequence of, coronary heart disease.

Many good systematic reviews have been published which focus on depression and its association with coronary heart disease progression. I therefore found that it was not necessary to go back to the original cohort studies for this part of my literature review. I used criteria adapted from Oxman, Cook & Guyatt's article on 'How to use an overview' (Oxman et al

1994) to identify five systematic reviews and two observational studies published between 1999 and 2005 [Tables 5:1 and 5:2] which were relevant to this research, because they reported on depression as a risk factor for coronary heart disease progression.

Table 5:1 Systematic Reviews of studies in pre-existing coronary heart disease focusing on depression and survival

Authors, year, country	Dates of search period	Question to answer	Sample	Inclusion/exclusion criteria	Total no of studies [overlap studies]	Depression measures	Outcomes measured	Summary of conclusions & comments
Hemingway & Marmot 1999 United Kingdom	1970-1999	Psychosocial factors in prognosis of coronary heart disease [CHD]	Post MI Angio-graphic coronary disease	Prospective cohorts 100 participants per study.	6[4]	2x Interviews  3x Self report questionnaires	All-cause mortality Cardiac mortality Nonfatal MI Recurrent angina Rate of premature contractions per hour Depressive symptoms Depressive disorders	3 studies with p<0.05, showed a strong prognostic association between the prevalence of depressive disorders and pre-existing coronary heart disease. 2 studies had used interviews to detect depressive disorders. Relative risk [RR] for angina at follow up was 3.12 [95% CI 1.58 ,6.16] (Ladwig et al 1994). OR 6.64; [95% CI 1.76, 25.09] when adjustment included >10 premature ventricular contractions per hour (Frasure-Smith et al 1995). These 2 studies followed up patients for <2 years.  The 3 <sup>rd</sup> study, follow up period (Denollet et al 1996) was 8 years. OR 2.69 [95%CI 1.33,5.45] for patients with disease detected by angiography.  2 of the studies which reported a moderate association between depression and pre-existing disease, had much longer follow up periods 12-19 years, and focused on depressive symptoms assessed via questionnaires. Overall females <22% representation.



Authors, year, country	Dates of search period	Question to answer	Sample	Inclusion/ exclusion criteria	Total no of studies [overlap studies]	Depression measures	Outcomes measured	Summary of conclusions & comments
Wulsin 2004 United States	1966- 2002	Epidemiologi- cal evidence for depression as a major risk factor for CHD	Post MI CHD + some CV disease	Population samples up to 5600 ≥ 100 participants per study.  Depression assessed by validated measures	27[15]	12x Interviews  19x Self report questionnaires  2x Physician diagnosis  1x Observer rating  Some used both	CV mortality Depressive symptoms Depressive disorders	Effect of depression in CHD may be restricted to a particular depressive disorder, such as unipolar depression or may be related to a variety of depressive disorders, or to a single depressive symptom such as fatigue.  Lack of evidence that treating depression reduces cardiac risk.  Most studies post MI.  May have omitted unpublished negative studies. Searched English databases only.
van Melle 2004 The Netherlands	1975- 2003	Depression & cardiovascular prognosis [CV]	Post MI	Prospective cohorts  Mortality within 2 years post MI  Depression assessed by validated measures	22[19]	9x Interviews  13x Self report questionnaires  Some used both	All-cause mortality Cardiac mortality CV events Depressive symptoms Depressive disorders	19 studies assessed depressive symptoms, 10 assessed depressive disorders. Some both. Short term mortality only considered within 2 year period post MI.  Few females included in the studies, so results more generalisable to males.  All participants under 74 years.  Reported that post MI depression, defined as either depressive symptoms or disorders and differentiated from non depressed, is associated with twice or 2.5 times increased risk of further CV events, all- cause and cardiac mortality but effect

Authors, year, country	Dates of search period	Question to answer	Sample	Inclusion/exclusion criteria	Total no of studies [overlap studies]	Depression measures	Outcomes measured	Summary of conclusions & comments
Barth 2004 Germany	1980-2003	To quantify the effect of depressive symptoms or disorders on mortality in CHD	Post MI Post CABG Post PTCA	Prospective cohorts  Depression assessed by validated measures	20[19]	4x Interviews  16x Self report questionnaires	All-cause mortality CV mortality Depressive symptoms Depressive disorders	greater in studies pre 1992 versus post 1992. OR 3.22 [95% CI 2.14,4.86] versus 2.01 [95% CI 1.45,2.78]  Depressed patients were twice as likely to die as non depressed  OR unadjusted 2.24, [95% CI 1.37,3.60] within the timeframe between initial assessment post event and a 2 year period.  Included studies with longer follow up  Search included German databases as well as English.
Frasure-Smith 2005 Canada	1989-2003 Focus on latest research published between 2001-2003	Is depression a CHD risk factor?	Post MI Post CABG Post angio-graphy Unstable angina CHD	Prospective cohorts  Reporting one outcome other than angina or chest	24[19]	10x Interviews  24x Self report questionnaires  Some used both	All-cause mortality Cardiac mortality CV mortality CV events Angina Depressive symptoms Depressive disorders	19 studies showed significant prognostic associations for worsening CHD  Most studies had follow up periods of less than 5 years, except Barefoot at 19 years (Barefoot et al 1996)  9/19 significant results for prognostic effect of depression on all-cause mortality (p<0.05)  Studies hard to compare because of variety of methodological differences.



### **5.3 Systematic reviews of observational studies**

The earliest review I found reported on five studies which focused on the effect of a range of psychosocial factors, including depression, on prognosis in coronary heart disease progression (Hemingway and Marmot 1999). The sample sizes from these studies ranged from 222 participants (Frasure-Smith et al 1995) to 1,250 (Barefoot et al 1996) all of whom had either suffered a myocardial infarction or had angiographic evidence of coronary heart disease. Depressive disorders were assessed by structured interview and depressive symptoms by self-report questionnaires. Two studies used standardised interview techniques to assess depression and the others used a variety of questionnaires which included the BDI and the Zung questionnaire. Mortality was an outcome measure in all studies except one in which recurrent angina pectoris was the main outcome (Ladwig et al 1994).

Results from three of the five studies, two of which had used structured interviews to assess depression, showed a strong prognostic association ( $p < 0.05$ ) between depressive disorders, and either morbidity or survival (Denollet et al 1996; Frasure-Smith et al 1995; Ladwig et al 1994), although the timings of the psychological assessments varied between the three studies.

Only one study had measured depression during hospitalisation (Frasure-Smith et al 1995) and this study showed that mortality was greatest in



depressed myocardial infarction patients when the number of premature ventricular contractions recorded had exceeded 10 per hour [OR 29.1; 95% CI, 6.97,122.07]. The finding that deaths were more common among depressed patients for whom more than 10 premature ventricular contractions per hour had been recorded was not surprising as it is well-known that premature ventricular contractions may provoke fatal cardiac rhythms. In Ladwig's study, depression was measured in post infarct patients at 3 weeks after hospitalisation. The main outcome measure was the new onset of anginal symptoms [RR 2.31 95% CI 1.58,6.16] (Ladwig 1994). On the other hand, Denollet assessed depression in patients with angiographic evidence of coronary heart disease during an outpatient CR programme and reported unadjusted results for cardiovascular mortality [OR 2.69 95% CI 1.33,5.45]. This study (Denollet 1996) had a follow up period of 8 years compared to the other two studies with follow-up of less than 2 years. It is clear that in all three studies (Denollet et al 1996; Frasure-Smith et al 1995; Ladwig et al 1994) depression strongly predicted mortality in patients with pre-existing coronary heart disease. However, this was not replicated in some of the other studies that followed participants for up to 19 years and where the effect of depression on mortality was shown to be weaker [RR 1.72 (p<0.05)] (Barefoot et al 1996).

Hemingway and Marmot's review has several limitations. Firstly, not all the studies had data on psychological morbidity prior to the index event. Secondly, a variety of covariates had been adjusted for in most of the studies

but none were common to all; three studies had adjusted for the effect of age. Thirdly, most studies reported on the presence of depressive symptoms, but not isolated major depressive episodes. Fourthly, depression was assessed with a variety of instruments at various stages during the recovery period. Finally, females were poorly represented in all the studies. For all these reasons it is not possible to draw exact comparisons between the studies included in this review.

One component of a comprehensive systematic review published five years later (Wulsin 2004) was an assessment of the strength of epidemiological evidence for depressive disorders or depressive symptoms as major independent risk factors in coronary heart disease progression. Wulsin's review included twenty-seven cohort studies from Europe and North America which were published in English over a 30 year period between 1972 and 2002. Inclusion criteria encompassed a wide range of depressive disorders such as bipolar depression and adjustment disorder with depressive mood. The main outcome measure relevant to my thesis was depression associated with coronary mortality. Depression was assessed in several ways. Twelve studies used structured interviews, most commonly the Diagnostic Interview Schedule, and the remainder used a selection of self-report questionnaires of which the BDI was used in over a third of all the studies. Some studies had used both questionnaire and structured interview as assessment tools, which were administered consecutively during a single psychological assessment (Connerney et al 2001; Lesperance et al 2000; Penninx et al 2001; Romanelli



et al 2002). Fifteen studies had controlled for a range of coronary risk factors that may have acted as confounders. The follow up period for the studies ranged from one month (Silverstone 1990) to 19 years (Barefoot et al 1996). The numbers of participants recruited to the studies varied from 52 patients post-angiography (Carney et al 1988) to 5,623 case control patients in General Practice (Hippisley-Cox et al 1998).

Between 10-22% of participants, the majority of whom had been diagnosed with myocardial infarction, were reported to have depressive disorders at the time of the onset of their acute coronary illness. This is over double the rate expected to occur within the general population (Lavie et al 1999) but similar to levels of depression in coronary patients reported previously by other researchers (Frasure-Smith et al 1993; Lett et al 2004; Schleifer et al 1989).

The reported prevalence of depressive disorders and symptoms varied between studies. Lesperance et al using the BDI and a structured interview found 41.4% of 430 patients who had been admitted to a Canadian hospital with unstable angina were suffering from either depressive symptoms or disorders (Lesperance et al 2000). On the other hand, Mayou et al using the Hospital Anxiety and Depression Scale (HADS) questionnaire in 347 myocardial infarction survivors in England found only 7.6% of his cohort had depressive symptoms at baseline (Mayou et al 2000).



The prevalence of depression also varied according to cardiovascular diagnosis. For instance, depression was most common in myocardial infarction patients [16-22%] and least common in those diagnosed with unstable angina [15%]. One study found a 20% prevalence of depressive disorders in patients who had undergone coronary artery bypass grafting (Connerney et al 2001).

Lesperance using the BDI (Lesperance et al 2000) and Penninx using structured interviews and a self report questionnaire (Penninx et al 2001), reported significant differences depending upon how depression had been categorised. In the more severely depressed patients Lesperance reported a six-fold increase in cardiac mortality [adjusted OR 6.73; 95% CI 2.43,18.64] while Penninx found a three-fold increase in patients with severe depression [RR 3.0, CI 1.1,7.8].

Eleven studies looked at the duration of depressive episodes in relation to each acute coronary event. Several studies found that post-coronary depressive episodes lasted for at least three months and often far longer following the index coronary event. Two studies reported the duration of depressive symptoms to last between up to one and a half years after an infarction; 34% of 70 myocardial infarction survivors were found to be depressed at their 12 month follow up (Travella et al 1994) and in an earlier study, a similar proportion of 101 post infarction CR attendees continued to

be severely depressed when assessed 18 months later ( $p > 0.001$ ) (Kavanagh et al 1975).

Results from Wulsin's review (Wulsin 2004) showed a prognostic effect for depression on cardiovascular mortality in 15 out of 25 studies. However, one important limitation in this review was that females were poorly represented in all the studies. In addition, although the review included two major studies which did not find an association between post myocardial infarction depression and mortality (Lane et al 2002; Mayou et al 2000), other smaller studies with negative outcomes or those published in languages other than English may have been omitted.

Van Melle and co-authors included Japanese studies in a meta-analysis, (van Melle et al 2004) which reported on 22 studies of coronary patients who underwent psychological assessment during the first three months after their index coronary event. Three quarters of study participants were male, and all were under 75 years of age. Depression was measured by self-report questionnaires and structured psychiatric interviews or a mixture of the two. Studies that used non-validated measures of depression were excluded. Outcome measures were cardiovascular prognosis and mortality within the 2-year period post infarction. At baseline the prevalence of depression ranged from 5 to 47 percent. In two studies 45% of myocardial infarction survivors were found to have either major [18%] or minor depression [27%] when assessed within eight to ten days of their event (Frasure-Smith 1995;



Schleifer et al 1989). One reason for this difference in reported rates of depression may be due to differences in whether depression was defined according to diagnostic criteria, or on the basis of a score on a questionnaire designed to elicit depressive symptoms. In some studies, the research carried out by Lesperance in 2000, Connerney in 2001, Penninx in 2001 and Romanelli in 2002, depressive symptoms and disorders had been assessed using both questionnaire and structured interview whereas other studies had relied on a variety of different questionnaires, rather than a single instrument.

Results from van Melle's research showed that patients with post infarct depressive disorders assessed at an early stage of coronary illness, were at significantly increased risk of death from all causes [OR 2.38, 95% CI 1.76,3.22 ( $p<0.00001$ )] and to a greater extent from cardiac mortality [OR 2.59, 95% CI 1.77,3.77 ( $p<0.00001$ )] during the 2-year follow up period from their initial coronary event. Depressed patients also experienced a greater number of cardiovascular events during follow-up [OR random 1.95, 95% CI 1.33,2.85 ( $p=0.0006$ )] although this effect was stronger for studies conducted before 1992, (old studies versus new  $p=0.08$ ). One possible explanation for this difference in these effects pre and post 1992, is that treatments for coronary patients, including CR, have improved in recent years (Blumenthal et al 2004). However, a limitation of all the studies was the lack of information on any of the patients regarding pre-infarct psychological morbidity. There was no way of knowing how many of them already had a history of depression prior to their coronary event.



In the same year, Barth and colleagues' meta-analysis examined the effect of depression on mortality in myocardial infarction survivors and also in patients who had undergone recent coronary revascularisation (Barth et al 2004). They included papers published between 1980 and 2003 from German as well as English databases. Depression was assessed at baseline entry to the studies by questionnaires or structured interviews or a combination of the two. The minimum follow-up period for each study was 3 months. Twenty studies were reviewed. Nine studies reported results that were adjusted for potential confounders such as smoking habit, age, gender, hypertension, dyslipidaemia<sup>ii</sup>, body mass index, previous angina, Killip class<sup>iii</sup> (Khot et al 2003) and previous infarction.

Results from this meta-analysis showed that depressive symptoms increased the risk of mortality. In the short term, with follow up over 5 years, unadjusted results showed that the participants with depressive symptoms were twice as likely to die compared with the non-depressed [OR 2.24, 95% CI 1.37,3.60]. However, in the long term beyond a five-year period, the effect of depressive symptoms on mortality was lower [OR 1.78, 95% CI 1.12,2.83]. Results that were adjusted for the known coronary risk factors also showed an effect of depressive symptoms on mortality rates [OR 1.76, 95% CI

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<sup>ii</sup> Dyslipidaemia is a disturbance in the amount of blood lipids

<sup>iii</sup> Killip's class is a risk stratification classification. Class I represents no evidence of heart failure. Class II represents symptoms of mild heart failure, râles involving a third or less of the posterior lung fields and a systolic blood pressure  $\geq$  90mmHg. Class III patients have overt pulmonary oedema, and class IV patients have cardiogenic shock and a systolic blood pressure < 90mm Hg.

1.27,2.43]. By contrast, for depressive disorders the effect on mortality was non-significant in the first 6 months post event, but became significant over the subsequent 18 months [OR 2.61, CI 1.53,4.47]. Only three studies reported adjusted results for depressive disorders [HR 4.29, 95% CI 3.14,5.86].

There were several limitations in this review. Firstly, the pre-event psychological health of participants was not known. Secondly, a variety of instruments had been used in the studies to assess depression. Thirdly, the timings of assessments varied depending on whether the entry criteria for the study included stable coronary disease, an acute coronary event or a revascularisation procedure. Finally, the levels of significance varied in the studies depending upon whether the results obtained had been adjusted for potential confounders or not. Only nine of the twenty studies reported adjusted results. The majority of patients in the studies were male and all were under the age of 75 years. These factors make it difficult to compare results and therefore to generalise the findings.

The most recent review of studies on depression and coronary heart disease concentrated on research published between 2001 and 2003 (Frasure-Smith and Lesperance 2005). Twenty-four prognostic studies from this review were relevant to this thesis because they reported mortality as an outcome. All these studies have been included in one or more of the reviews I have already described. Outcome measures included the presence of anginal



symptoms or heart failure, nonfatal cardiovascular events and mortality. Results were reported as adjusted or non-adjusted and as significant with a p value less than 0.05 or as zero when non-significant. The effect sizes were not summarised in this paper.

The majority of studies had follow up periods of less than 5 years but the study with the longest follow up of over 19 years which I have already referred to in this chapter, was also included in this review (Barefoot et al 1996). In 19 studies, the researchers found a significant association ( $p < 0.05$ ) between depression and worsening of coronary heart disease. Nine of the 19 showed a significant effect for depression on mortality.

There were methodological differences between many of the studies. One of several limitations was an inconsistency in the types of instruments used to measure depression. In addition, when adjusted results were reported these were based on a variety of different covariates, but were commonly the coronary risk factors: diabetes, obesity and hypertension. It is difficult to compare the adjusted results between each study because the covariates were not the same for each study. Other inter-study differences included different sample sizes and demographic data, different timings for assessment of depression, different definitions of depression and different ways of reporting outcomes. Some studies reported multiple outcomes, such as mortality and nonfatal events, whereas others had single outcomes and only reported on all-cause mortality. Inaccurate certification of deaths and



coding errors may also have influenced some of the studies' results. The change from ICD-9 to ICD-10 has given rise to a number of ill-defined cardiovascular codes which have been reported to be inaccurately assigned to ischaemic coronary deaths (Lozano et al 2001). Such discrepancies, which I also discuss in Chapter 8 page 210, may affect mortality data reporting in the studies that were conducted during the changeover period between ICD-9 to ICD-10. This review omitted to include one of the two main studies with negative findings (Mayou et al 2000).

#### ***5.4 Observational research published after the systematic reviews***

Two observational studies on depression and coronary heart disease were not included in the systematic reviews because they have been published recently.

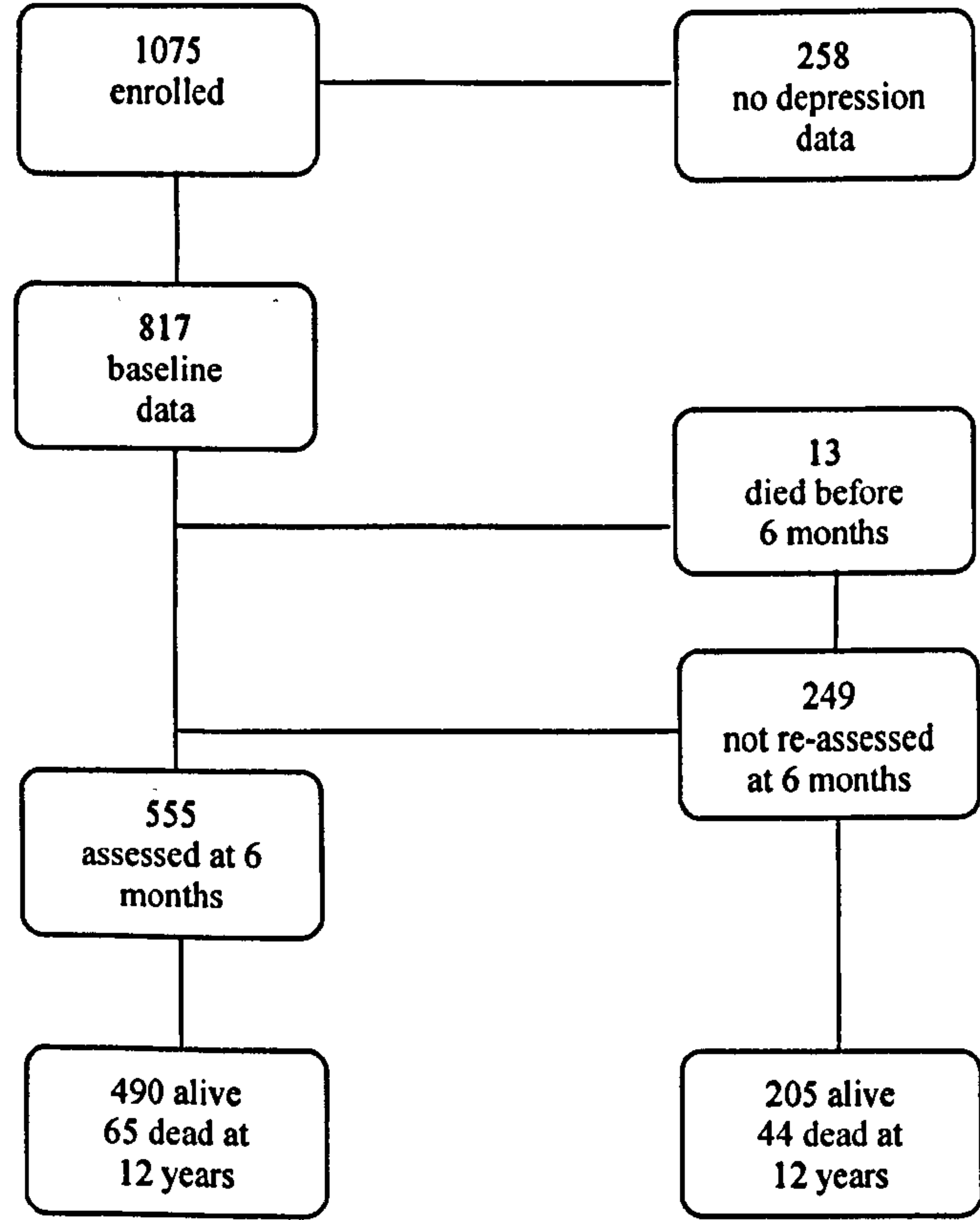
Table 5:2 Eligible observational studies that have incorporated measures of cardio-respiratory fitness and mortality or cardiovascular events as main outcomes

Authors Year Country	Study objective	Eligible	Participants  % Female	Mean Age	Depression Measures	Main outcomes evaluated	Period of follow up	Summary of conclusions and comments
Blumenthal et al 2003 USA	Depression associated with increased risk of mortality pre & post CABG	817/ 1075 CABG	27	61	Questionnaire CESDQ <sup>v</sup> day before surgery and at 6/12	All-cause mortality Depressive history pre surgery	12	Many excluded from those eligible  Pre-surgical depression adjusted HR 2.4 [95% CI 1.4,4.0] Persistent depression for > 6/12 HR 2.2 [95% CI 1.2,4.2] versus no depression. 15% deaths
Grace et al 2005 Canada	Effect of depression post diagnoses ACS <sup>v</sup>	750/ 1800 ACS	35	62	BDI once during hospital admission between day 2 and day 5	All-cause mortality Depressive history Depressive symptoms	5	Onset of depression during hospitalisation had greater adjusted HR 4.59 [95% CI 1.62,13.01] compared with HR for those with pre-morbid depression or persistent depression HR 1.90 [95% CI 1.12,3.24] at 2 years HR 1.53 [95% CI 1.04, 2.24] at 5 years. 15% deaths

<sup>iv</sup> CSEDQ Center for Epidemiological Studies Depression Questionnaire  
<sup>v</sup> ACS Acute Coronary Syndrome

This first study (Blumenthal et al 2003) was one of a few observational studies that looked at survival outcomes and depression after coronary bypass graft operations. Patients with severe co-morbid conditions and those who were undergoing other cardiac surgery such as valve replacements were excluded from the study. In addition, patients who refused to complete the questionnaire pre-surgery were also excluded, as were those who had a prior diagnosis of psychiatric disorder. A total of 817 participants [27% females] were enrolled in the study and completed a baseline depression assessment. Depression was assessed using the CES-D (Radloff 1977) the day before surgery and at six months post surgery. The cohort was followed up for 12 years [Figure 5:1].

**Figure 5:1 Study Profile from Blumenthal et al 2003**





Survival analyses, which controlled for a number of potential confounders such as age, gender, the known coronary risk factors, the number of bypass grafts, previous myocardial infarction, and left ventricular ejection fraction were performed using a Cox proportional hazards model. Early deaths that occurred within 30 days post surgery were excluded from the survival analyses. Depressive symptoms were treated initially as a binary variable and later assigned into one of four categories: a never depressed category, depressive symptoms found at baseline that lasted for less than six months, no depression at baseline but new onset of symptoms within six months, and persistent symptoms of depression at baseline and beyond a six-month time frame. Thirty-four percent of participants did not complete a second assessment.

At baseline 26% of the cohort was found to have moderate or severe symptoms of depression and 12% mild symptoms. More females than males had reported depressive symptoms ( $p < 0.001$ ). At the end of the follow up period 15% of the cohort had died. This study showed that the presence of depressive symptoms pre-surgery increased the risk of mortality in the 12 years post surgery ( $p = 0.001$ ) [adjusted HR 2.4, 95% CI 1.4, 4.0]. Those whose depressive symptoms persisted beyond the first six months post bypass were also at a higher risk of death during the 12 year follow-up period [adjusted HR 2.2, 95% CI 1.2, 4.2 ( $p = 0.015$ )].

The main limitation of this study was that only 50% of eligible participants attended the follow up assessment at 6 months. One-quarter of patients were not enrolled into the study because they were too sick or debilitated to take part, although the researchers do not explain how they defined the term sick. These findings are therefore not generalisable to all people who have undergone coronary bypass procedures.

Grace and co-researchers (Grace et al 2005) examined the effect of depressive history and symptoms on mortality in an observational study of 750 participants [35.2% females], mean age 61.6 years, who were assessed for depression in a selection of Canadian coronary care units following a diagnosis of an acute coronary syndrome between 1997 and 1999. Nine hundred and ten patients (50.6%) from the initial 1,800 patients who were approached to join the study, agreed to participate. Participants were followed up for 5 years.

Information on co-morbidity was provided by a link to a Discharge Abstract Database and co-morbidity scores were computed using the Charlson Co-morbidity Index (Charlson et al 1987). Depressive symptoms were assessed using the BDI questionnaire, administered on one occasion, during the hospital stay between day 2 and day 5. Former depressive history, lasting for more than two weeks, was established from each participant. Depression scores were treated as a binary variable with scores either less than 10 or 10 and above. Survival analyses were performed using Cox proportional



hazards models which were adjusted for age, gender, income, marital status, education level, diagnosis, systolic blood pressure, smoking, Killip class, co-morbidity, diabetes, myocardial infarction and heart failure.

The 836 participants finally enrolled in the study were significantly younger than the participants in the original cohort, and more likely to be married and male ( $p < 0.001$ ). At baseline assessment, 23% of participants reported a history of depressed mood prior to hospital admission and 31% had raised depression scores at the time of their index event. Fourteen per cent were found to be persistently depressed. Females were more likely than males to have a raised depression score. Fifteen per cent of the cohort died during the 5-year follow up period. Depressive symptoms assessed during the hospital stay, defined as a BDI score of  $\geq 10$ , were predictive of mortality at two years post event, [adjusted HR 1.90, 95% CI 1.12,3.24] and at 5 years [HR 1.53, 95% CI 1.04,2.24]. Those with a previous history of depression that did not worsen during the acute illness had the lowest mortality rate. This was in contrast to the reported hazard ratio from a new onset of depression, reflecting a first episode of depression recorded during the hospital stay, which was far greater [HR 4.59, 95% CI 1.62,13.01].

This study showed that the onset of depressive symptoms during an acute coronary event is of prognostic importance. It also indicated that acute coronary syndrome patients with a previous history of depressive symptoms which did not worsen whilst they were in hospital fared better than those who



experienced a new onset of depression at the time of the event. Two earlier studies had also assessed pre-event depressive history and reported similar findings (Berkman et al 1992; Bush et al 2001). It is hypothesised that past psychiatric history may not be as relevant to survival as the severity of depressive symptoms recorded during an acute event.

Although significantly more men participated in this study [64.8%] ( $p < 0.001$ ) there was a better representation of females [35.2%] in this study than in many others that have been published. Another feature of the study was that Grace et al assessed participants' co-morbid illness using the Charlson Comorbidity Index (Charlson et al 1987) and accounted for co-morbid conditions in the regression models. This is important because co-morbid illness may affect function and survival and may be a confounding factor in assessing risk of mortality. The proportion of participants found to be depressed at baseline was similar to levels reported by other researchers. The proportion of reported deaths from all causes over the follow up period was also comparable to the level reported from a study of revascularisation patients (Blumenthal et al 2003) although the researchers did not report on cardiovascular mortality in this study. The main weakness of this study was the loss of over half of potential recruits at the start of the study, which means that the results may not be generalisable to all acute coronary syndrome patients who undergo psychological assessments during the hospital stay.

## **5.5 Summary**

There is an interesting picture emerging concerning the part depression plays as a risk factor in coronary heart disease progression. Nearly all the observational studies have shown that the presence of depressive symptoms or depressive disorders at the time of an acute coronary episode or coronary procedure may adversely affect morbidity and survival. However, there are two studies of myocardial infarction survivors with negative outcomes and which did not show the presence of in-hospital depression to predict survival (Lane et al 2002; Mayou et al 2000). Both these studies, using different questionnaires to assess depression, [Mayou had used the HADS and Lane the BDI] were performed in the United Kingdom. In some groups of coronary patients depression has been shown to predict the recurrence of cardiovascular events.

It is hard to make comparisons between studies and to draw conclusions from those that have been published to date. The reasons for this include the type and timing of psychological assessment, the way baseline prevalence of depression is assessed, and the difference in outcomes measured. Table 5:3 shows a number of the studies mentioned in this chapter together with the method used to determine psychological state and the differences in some of the other parameters recorded. The odds ratios quoted vary from 1.26 [95% CI 1.07,1.48] (Barefoot et al 1996) to 7.82; [95% CI, 2.42, 25.26] (Frasure Smith et al 1995) and were likely to have been affected by several factors. These include the length of follow up period of

individual studies, whether assessment covered depressive symptoms and/or depressive disorders, the outcomes assessed [deaths from all causes, cardiovascular deaths or cardiovascular events], and whether the results reported were adjusted for potential confounders. Nevertheless, across the many different measures in use for diagnosing either depressive symptoms or disorders, most studies consistently found the presence of depression to be related to worsening of coronary symptoms and increased mortality in spite of the variation in instruments used



Table 5:3 Comparison of studies and reviews that have incorporated measures of depression, mortality and cardiovascular events as main outcomes

Author, year	Follow up, years	Depression measure	Timing of assessment/diagnosis	Baseline prevalence of depression	Outcome	Effect measure
Carney 1988	1	Interview	Out patients post angiogram	17% disorders	All-cause mortality	OR 2.65 [95% CI 0.21,31.46] [Non-adjusted]
(Ahern et al 1990)	12	Questionnaire BDI	6-60 days post MI + arrhythmias	40% symptoms	All-cause mortality	RR 1.3 (p<0.05)
Ladwig 1994	6 months	Interview	3 weeks post MI	15% disorders	Recurrence of angina	RR 2.31 [95% CI 1.58,6.16]
Frasure-Smith 1995	1.5	Interview Questionnaire BDI	In hospital MI	16% disorders 32% symptoms	Cardiovascular mortality	OR 7.82 [95% CI, 2.42, 25.26] [Non-adjusted]
Denollet 1996	8	Questionnaire Type D	Outpatients with angiographic CHD	41.9% symptoms	Cardiovascular mortality	OR 2.69 [ 95% CI 1.33,5.45] [Non-adjusted]
Barefoot 1996 and 2000	19.4	Questionnaire Zung	Out patients CHD	11.1% symptoms	Cardiovascular mortality	OR 1.26 [95% CI 1.07,1.48] [Non-adjusted]  HR 1.42 [95% CI 1.14,1.76] [Adjusted]
Mayou 2000	1.5	Questionnaire HADS	In hospital MI	7.6% symptoms	All-cause mortality	OR 1.64 [ 95% CI 0.64,4.20] [Non-adjusted]
Lesperance 2000	1.5	Questionnaire BDI	In hospital unstable angina	41.4%	Cardiovascular mortality Nonfatal myocardial infarction	OR 6.73 [95% CI 2.43,18.64]] [Adjusted]

Author, year	Follow up, years	Depression measure	Timing of assessment/diagnosis	Baseline prevalence of depression	Outcome	Effect measure
Penninx 2001	4.2	Questionnaire CESD	Out patients CHD	19.7% symptoms	Cardiovascular mortality	RR 1.6 [95% CI 1.0,2.7] [minor depression]  RR 3.0 [95% CI 1.1,7.8 ] [major depression]
Connemey 2001	1	Interview	Before discharge post CABG	20.3% disorders	Cardiovascular mortality	RR 2.3 [95% CI 1.17,4.56]
Lane 2002	3	Questionnaire BDI	In hospital MI	30% symptoms	Cardiovascular mortality	OR 1.15 [95% CI 0.49,2.70] at 1 year [Non-adjusted]  OR 0.84 [ 95% CI 0.37,1.91] at 3 years [Non-adjusted]
Blumenthal 2003	12	Questionnaire CESD	Day before CABG	12% severe depression 26% mild depression	All-cause mortality	HR 2.4 [ 95% CI 1.4,4.0] at baseline  HR 2.2 [95% CI 1.2,4.2] persistent > 6 months
van Melle 2004	2	Varieties of Interviews or/and Questionnaires	MI	Range 5-47% mix of symptoms and disorders	All-cause mortality Cardiovascular mortality Cardiovascular events	OR 2.38 [95% CI 1.76,3.22] [all-cause mortality]  OR 2.59 [95% CI 1.77,3.77] [cardiovascular mortality]  OR 1.95 [95% CI 1.33,2.85] [cardiovascular events]  OR 3.22 [95% CI 2.14,4.86] for studies pre 1992  OR 2.01 [95% CI 1.45,2.78] for studies post 1992

Author, year	Follow up, years	Depression measure	Timing of assessment/diagnosis	Baseline prevalence of depression	Outcome	Effect measure
Barth 2004	Up to 15 years	Varieties of Interviews or/and Questionnaires	MI, CABG, PTCA	Not stated	All-cause mortality Cardiovascular mortality	OR 2.24 [95% CI 1.37,3.60] for depressive symptoms [unadjusted]
						OR 1.76 [ 95% CI 1.27,2.43] for depressive symptoms [adjusted for risk factors and in longer term]
						OR 2.61 [95% CI 1.53,4.47] for disorders after 2 years
Grace 2005	5	Questionnaire BDI	In hospital ACS	31.3% symptoms	All-cause mortality	HR 4.59 [95% CI 1.62,13.01] for new onset depression at baseline
						HR 1.90 [95% CI 1.12,3.24]. pre-morbid depression or persistent depression at 2 years
						HR 1.53 [95% CI 1.04,2.24] at 5 years



Many of the studies showed that depression occurring at the time of a coronary event increases the risk of mortality. Some studies also show that the hazard ratio for mortality in patients diagnosed with depression usually but not always decreases over time when reported over a 2 to 19 year follow-up period.

The risk of death for depressed patients with coronary disease is also increased when other factors are taken into account. For example, new onset depression is greatest in patients when the number of recorded premature ventricular contractions exceeds ten per minute (Frasure-Smith et al 1995). In contrast, the risk of death is less when the presence of chronic depressive symptoms or disorders exists before the coronary event (Berkman et al 1992; Bush et al 2001; Grace et al 2005).

One difficulty in summarising the research on depression and coronary heart disease has been that most of the research carried out prior to 1990 concentrated on male myocardial infarction survivors. Van Melle (van Melle 2004) found that the effect of depression on mortality was stronger in the earlier studies. Studies published after 1992 have tended to incorporate other aspects of both acute and stable coronary heart disease and have better representation of females. They may also have been affected by the improved access to more effective pharmacology for coronary and psychiatric illnesses and in the United Kingdom partly influenced by the

Department of Health's publication of the National Service Framework for Coronary Heart Disease (DOH 2000).

However, the exact nature of the biological mechanisms thought to provoke coronary heart disease progression in relation to depression remains unclear. Many hypotheses have been tested within the last five years that attempt to clarify the relationship between depression and the pathophysiology of coronary heart disease progression; I examine some of these in the next chapter.

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## **Chapter 6**

# **Pathophysiological mechanisms associated with coronary heart disease and depression**

### ***6.1 Introduction***

Many hypotheses have been proposed to explain observed associations between depression and cardiovascular disease. This chapter considers studies which have examined the pathophysiological mechanisms of this association.

#### **6.1.1 Lifestyles, behaviour and depression**

There are several lifestyle and behavioural factors associated with symptoms of depression or depressive disorders, which have been shown to contribute to poor outcomes in coronary patients. Depression and social isolation for instance are thought to affect the pathogenesis of atheroma (Rozanski et al 1999), as both may lead to the adoption of unhealthy behaviours. Other behavioural factors associated with depression in the coronary population also affect outcomes. Coronary patients who continue to smoke are less likely to complete a CR programme (Oldridge et al 1983), more likely to continue to smoke post event, and have a higher re-infarction rate (Ladwig et al 1994)

Depressed patients are less likely to complete CR. In an observational study in our CR programme we reported a drop out rate of 12.6% and in common with other researchers (Glazer et al 2002), found that patients in our cohort who were clinically depressed at the start of Phase III CR were less likely to complete CR [OR 1.12, 95% CI 1.08,1.17 ( $p<0.001$ )] (Turner et al 2002). Depression has also been related to a failure to take up the offer of CR (Ades et al 1992) and may be responsible for coronary patients' delayed return to work, (Soderman et al 2003) impaired quality of life, (Ladwig et al 1994) as well as non-compliance with a range of medical treatments (Carney et al 1995a; DiMatteo et al 2000) and attendance at CR (Lane et al 2001). However, one reason for these poor outcomes may be due to depression acting as a marker for more severe cardiac disease.

### **6.1.2 Quality and provision of health care and depression**

Depression has been linked to a reduced access to optimal health care, which may consequently affect the speed and completeness of recovery from an illness. This was illustrated in a retrospective study of hospital records in the United States, which examined the uptake of angiography or revascularisation procedures in relation to psychological state. A cohort of 113,653 eligible participants aged 65 years or older, with a confirmed acute myocardial infarction were enrolled in the study between February 1994 and July 1995 during their hospital stay (Druss et al 2000). At baseline 5% of participants were found to have a broad range of co-morbid mental illnesses which included mood disorders, depressive symptoms or disorders and



schizophrenia. This study showed that the patients with mental disorders were less likely to undergo revascularisation procedures ( $p<0.001$ ) than the patients without mental disorders. However, it was not clear whether patient or provider factors were responsible for the difference in uptake, which could have several causes. Firstly, depressed patients may be less likely to seek or attend for treatment. Secondly, health professionals from the provider unit may not offer or prioritise treatment for patients with mental disorders. Finally, it may be that the treatment of mental illness such as depressive symptoms or disorders is given a higher priority than the coronary procedure. However, because the researchers had included a wider range of mental disorders than simply depressive disorder or symptoms the findings are hard to quantify.

Depressive symptoms have also been shown to influence convalescence in coronary heart disease patients (Mallik et al 2005). Over a two-year period 963 patients were followed up after coronary bypass surgery and were assessed for physical function at baseline and at six months, using the physical component of the SF36<sup>i</sup>, and the self-report Geriatric Depression Scale<sup>ii</sup>. At baseline assessment 8% of the cohort scored highly on the Geriatric Depression Scale with scores greater than 10, and 17% had moderate scores of between 5 and 9. Participants with depressive symptoms reported greater co-morbidity and worse physical functioning. At the six-month assessment and after adjusting for coronary heart disease

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<sup>i</sup> SF-36 is a 36 – item questionnaire focussing on quality of health

<sup>ii</sup> Geriatric Depression Scale: Range 1-15 representing total number of depressive symptoms



severity, baseline SF36 scores and medical history, depressive symptoms independently predicted a failure to improve functional capacity ( $p=0.002$ ), during the convalescent period.

### **6.1.3 The Inflammatory process, atherosclerosis and depression**

Coronary heart disease is considered to be a chronic inflammatory disease (Appels et al 2000; Libby 2002) with endothelial inflammation in the coronary arteries as a precursor of atherosclerosis (Annikue et al 2005). However, it is not clear whether markers of the inflammatory process, such as soluble intercellular adhesion molecule 1, interleukin-6 and C-reactive protein are raised in coronary heart disease because of coronary plaque instability or rupture within the endothelial wall of the coronary artery, or whether the inflammatory process provokes the plaque rupture in the first place. When coronary patients are treated with anti-inflammatory medication this does not seem to reduce the endothelial inflammation. Moreover, the use of the highly selective anti-inflammatory drugs known as Cyclo-oxygenase [COX] 2 inhibitors appears to increase cardiovascular risks in some patients (Bombardier et al 2000), as demonstrated in the VIGOR<sup>iii</sup> study.

The VIGOR study was the first study to question the safety of COX-2 inhibitors. The researchers examined the upper gastrointestinal toxicity of rofecoxib [Vioxx], a COX-2 inhibitor, and naproxen in patients with rheumatoid arthritis (Bombardier et al 2000) over a follow-up period of nine

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<sup>iii</sup> VIGOR : Vioxx gastrointestinal outcomes research

months. Although the group who received 50mg/day of rofecoxib reported 50% less gastrointestinal symptoms, they also experienced a greater number of cardiovascular events than the naproxen group. The incidence of myocardial infarction was noticeably higher in the patients receiving rofecoxib when compared to the group who were given 1000mg/day of naproxen [RR 2.37, 95% CI 1.39,4.06] for rofecoxib versus naproxen. There are two possible reasons for this. Firstly, the inhibitory role of COX-2 leaves patients more vulnerable to pro-thrombic events. Secondly, rofecoxib may have a detrimental effect on blood pressure levels in susceptible patients and thus provoke a cardiovascular event. The safety profile of COX-2 inhibitors is not fully established. Current practice is to use them with caution in coronary patients, whilst further studies and systematic reviews are continuing to examine their safety (Juni et al 2004). It has been suggested recently that naproxen plus a proton pump inhibitor is a safer anti-inflammatory option than the COX-2 inhibitors that are currently available (Graham 2006).

Several studies have focused on the interaction between the inflammatory process and the formation and progression of atheroma. A small study (Appels et al 2000) examined the serological nature of endothelial inflammation by taking samples from 30 male angioplasty patients who had been diagnosed with severe but stable angina but who did not present with an overt inflammatory disease at baseline. The researchers used a structured interview [the SCID<sup>iv</sup>] to assess depressive disorders and the

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<sup>iv</sup> SCID: a structured interview technique



Maastricht Interview [MIVE<sup>v</sup>] to assess Vital Exhaustion which they thought might be linked to depressive symptoms. The study participants were two groups. After assessing psychological state, 15 participants formed a group who appeared to be suffering from exhaustion and the second group was composed of 15 non-exhausted patients. One patient dropped out of the study. Results from this study showed that the samples taken from the exhausted group had significantly higher levels of two inflammatory markers; interleukin -1 $\beta$  (p=0.001) and tumour necrosis factor (p=0.04) than the levels in the non-exhausted group. This indicated that the mental state of participants was linked to the presence of interleukin -1 $\beta$  and to a lesser extent, tumour necrosis factor. It remains unclear, however, whether exhaustion with or without depressive symptoms triggers coronary endothelial inflammation, or whether an inflammatory process, occurring within a coronary artery is responsible for provoking or worsening the symptoms of depression.

Endothelial dysfunction has also been examined by Broadley and co-researchers (Broadley et al 2002) in a small group of patients being treated with antidepressant therapy. The ten participants were matched to a group of 'healthy' controls. Endothelial function was assessed by measuring flow-mediated dilation in the brachial artery. This study found that seven of the ten participants being treated with antidepressants had impaired arterial endothelial function, compared with the control group whose endothelial

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<sup>v</sup> MIVE: a tool for recognising Vital Exhaustion



function remained unimpaired ( $p=0.005$ ). There are two possible explanations for these results. Firstly, depressive episodes or depressive symptoms may adversely affect the normal condition of the endothelial tissue and consequently its function. Secondly, it is possible that the antidepressant medication was responsible for either provoking endothelial dysfunction or inhibiting the resolution of an on-going endothelial inflammatory process.

Several other researchers have also examined the strength of the association between coronary heart disease, depressive symptoms or disorders, endothelial dysfunction and inflammatory markers. For example, blood samples were collected from 481 patients who were diagnosed with depression during hospital admission with an acute coronary syndrome, shortly after discharge home (Lesperance et al 2004). Analyses were adjusted to account for gender, smoking and having metabolic syndrome<sup>vi</sup>. The results from this study showed that the group with depressive symptoms or disorders had higher levels of the soluble intercellular adhesion molecule 1 than the group who were not depressed. However, when the researchers looked at inflammatory markers in a subset from the same cohort, 46 in the non-depressed group and 57 in the depressed group, they were unable to find any between group differences. One drawback from this study was that 50% of eligible patients invited to take part in this study had declined and

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<sup>vi</sup> metabolic syndrome predisposes to coronary heart disease and features the following traits: central obesity, elevated blood fat levels, hypertension, insulin resistance and pro-thrombotic or pro-inflammatory state

therefore the study sample was not necessarily representative of a depressed coronary population.

The studies performed to date that have examined the association between depression, coronary disease and inflammatory markers have several limitations. Firstly, the size of the samples in most studies apart from one (Lesperance et al 2004) was small. Secondly, Lesperance et al were also the only researchers to adjust for potential confounders in their analyses, although these were limited to gender and smoking and the metabolic syndrome. Finally, it is possible that the results from some studies may have been influenced by other factors such as the use of statins or other medications. For example, Lesperance found that depressed patients not taking statin medications had higher levels of the inflammatory marker C-reactive protein than the non-depressed (Lesperance et al 2004). The available evidence therefore regarding the relationship between inflammatory markers and depressive symptoms in coronary patients has yet to be clarified.

#### **6.1.4 Dysregulation of the autonomic nervous system and depression**

Dysregulation of the autonomic nervous system may be another mechanism responsible for the underlying relationship between coronary heart disease and depression. In depressed patients with coronary disease, autonomic nervous system dysfunction has been shown to cause abnormalities in resting heart rates (Carney et al 1999), heart rate variability (Carney et al



1995b) and arrhythmias (Carney et al 1993) but little is known about the mechanisms involved in this association. It is speculated that the presence of depressive symptoms or depressive disorders gives rise to a reduced parasympathetic drive [parasympathetic tone is known to protect against arrhythmias] which allows the sympathetic nervous system to dominate cardiac innervation and thus give rise to chronically elevated resting heart rates. A recent study has focused on the relationship between autonomic dysfunction and depression by examining resting heart rates and heart rate variability in myocardial infarction survivors.

A group of 100 participants [23 female] with a mean age of 62 years were followed up for 5 years from January to December 1999 in Italy (Drago et al 2007). Depression was measured by structured interview measuring depressive disorder and the BDI assessing depressive symptoms. Heart rate variability was monitored by a 24 hour Holter recording. At baseline 15 patients were found to be suffering from a depressive disorder and 35 had mild to moderate depressive symptoms. More females than males had depressive disorder ( $p < 0.01$ ). A total of 98 patients was followed up, of whom 6% had died during the five years. The patients with depressive disorder were found to have higher heart rates ( $p < 0.01$ ) and also lower heart rate variability ( $p < 0.01$ ) than the patients without depression. Patients with a BDI score greater than 10, an indication of depressive symptoms, had lower heart rate variability ( $p = 0.01$ ) but not significantly higher heart rates. Statistical analysis included a multiple regression model which adjusted for



potential confounders; age, gender, diabetes, dyslipidaemia, previous myocardial infarction, anterior myocardial infarction, poor ejection fraction, acute thrombolysis, primary angioplasty and heart rate variability.

Drago's study confirmed that the patients with depressive disorders were at greater risk of all-cause mortality [OR 12, 95% CI 2.6,56 ( $p<0.01$ )]. It also indicated that heart rate variability was predictive of mortality ( $p<0.01$ ) as has been previously reported (Carney et al 2001). The mortality risk was greater for the patients with depressive disorders than those with mild or moderate depressive symptoms. However, the researchers were unable to show that autonomic dysfunction was related to an increased mortality risk for the depressed group during the study period. The main limitation of this study was its small sample size and low mortality rate. Only 6 deaths were reported during the five years of follow up.

Increased ventricular ectopic activity at rest (Cripps et al 1989) and during exercise (Weld et al 1981) are predictors of one-year mortality post myocardial infarction. Coronary heart disease may trigger arrhythmias, particularly during an evolving myocardial infarction. In a cohort of 103 patients with angiographic evidence of coronary disease, depression was assessed by structured interview and all patients in the group underwent 24 hour Holter monitoring (Carney et al 1993). Results were adjusted for gender, smoking status,  $\beta$  blocker and nitrate therapy. The researchers

found a higher prevalence of ventricular tachycardia<sup>vii</sup> in the 21 depressed patients [RR 8.2 95% CI 2.14,31.7 (p <0.008)] than the non-depressed, which was not related to either the severity of coronary disease or to ventricular function. There was also no difference in the prevalence of ventricular tachycardia between the patients who had met the criteria for major depression and those with minor depression. The main limitation with this study was its small sample size.

It is thought that there may be an association between depression, arrhythmias and mortality although survival outcomes are not improved by arrhythmia treatment. Anti-arrhythmic drugs, with the possible exceptions of  $\beta$  blockers (Group 1982) and amiodarone (Farre et al 1999) have not been shown to reduce mortality in myocardial infarction patients regardless of psychological state (Ruskin 1989).

### **6.1.5 Platelet dysfunction and depression**

The role of platelet activation in the progression of acute coronary syndromes and acute coronary thrombosis is clear. High levels of platelet activation may affect clotting mechanisms and increase the risk of further cardiovascular events in depressed coronary patients (Nemeroff and Musselman 2000). They have been linked to the evolving of an acute coronary syndrome or coronary thrombus. However, increased rates of platelet aggregation are found in people with coronary heart disease with or without depressive symptoms (Serebruany et al 2003).

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<sup>vii</sup> Ventricular tachycardia is a fast, potentially life-threatening arrhythmia



The use of the antidepressant medication sertraline, a selective serotonin reuptake inhibitor [SSRI] has recently been studied as it is known to inhibit platelet activity (Serebruany et al 2003). A substudy from SADHART<sup>viii</sup> (Glassman et al 2002) monitored the effect of antidepressants on platelet behaviour (Serebruany et al 2003). Fifty-four recent myocardial infarction survivors with diagnoses of depression were recruited to the study and randomised to receive sertraline or placebo. The participants were also taking standard antiplatelet medication; aspirin or clopidogrel. Blood samples were taken at baseline, and at 6 and 16 weeks. The results showed that the group treated with sertraline had statistically reduced platelet and endothelial activity ( $p=0.03$  and  $p=0.04$ ) compared with the group who had received the placebo. It was not known, however, whether the treatment impacted on physical or psychological outcomes as these had not been assessed.

## **6.2 Summary**

This chapter has given a brief overview of the potential pathophysiological mechanisms that may link coronary heart disease and depression. Despite the use of different approaches to assessing depression in many of the studies, it is well established that depression has an adverse effect on psychosocial behaviour (Carney et al 2002) and may consequently affect morbidity and mortality. Depression is associated with the adoption of unhealthy behaviours such as smoking or poor dietary habits or failing to

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<sup>viii</sup> SADHART – The Sertraline antidepressant heart attack randomized trial



complete a CR programme, which are likely to exacerbate the risk of relapse and disease progression (Ladwig et al 1994; Oldridge et al 1983; Rozanski et al 1999). However, research by Druss (Druss 2000) was unable to establish the extent to which this reflected a lack of service delivery to patients who have depression, rather than poor uptake and/or treatment adherence. Convalescence also appears to be adversely affected when depressive symptoms are present (Mallik et al 2005).

Although it has been hypothesised that depression is associated with inflammation and impaired endothelial function, evidence for this remains limited. The studies performed so far have only recruited small numbers of patients (Appels et al 2000; Broadley et al 2002) or succeeded in enrolling 50% of a study population into trials (Lesperance et al 2004). Additional research is awaited in this area to determine whether higher levels of inflammatory markers may discover a subgroup of depressed coronary patients who are at higher risk for succumbing to further coronary events.

Several studies by Carney et al have shown autonomic nervous system dysfunction to cause abnormalities in resting heart rates (Carney et al 1999), heart rate variability (Carney et al 1995b) and arrhythmias (Carney et al 1993) but the mechanisms responsible for this association are not clear. Future studies are also needed to focus on this, particularly because survival outcomes have not yet been shown to improve by the treatment of arrhythmias.

Platelet activation with increased rates of aggregation is found in coronary patients with or without depressive symptoms or disorders and is associated with the formation of coronary thrombi and the subsequent evolution of an acute coronary syndrome (Nemeroff and Musselman 2000; Serebruany et al 2003). Clinical depression is also associated with platelet dysfunction.

SSRIs are known to reduce platelet and endothelial activity in the coronary population. Results from recent studies indicate that the use of SSRIs as an adjunct to conventional anti-platelet therapy may improve cardiovascular outcomes.

In the final chapter of this literature review I discuss the role of antidepressant therapy and psychosocial interventions in coronary heart disease that are particularly relevant to the cohort in this study.

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## **Chapter 7**

### **The role of antidepressant therapy and psychological interventions in coronary heart disease progression**

#### ***7.1 Antidepressant therapy***

Few studies have looked specifically at treatments for coronary patients with depression although evidence of the prognostic role of depression in coronary disease progression is reasonably persuasive. Pharmacological treatments for depression are becoming increasingly prevalent in the coronary population, and there is preliminary evidence that non-pharmacological interventions such as aerobic exercise therapy and counselling may also be effective ways of managing coronary patients with depressive disorders.

The use of older tricyclic antidepressants is contraindicated in acute or unstable coronary disease because they are cardiotoxic and may provoke serious cardiovascular side effects (Serebruany et al 2003). They are known to increase heart rates, induce orthostatic hypotension and provoke conduction abnormalities (Roose and Spatz 1999). However, several recent randomised controlled trials have considered the efficacy and safety of SSRIs in patients with coronary heart disease. The majority of these studies enrolled small numbers of patients, with one exception.

The SADHART multi-centre randomised double-blind trial (Glassman et al 2002) examined the safety and effectiveness of treating depressed patients with unstable coronary heart disease by using SSRIs. This study examined the fate of 369 out of 556 eligible patients who had suffered an acute coronary syndrome or episode of unstable angina within the previous 30 days and were currently experiencing a major depressive disorder. They were randomised between 1997 and 2001 to receive either treatment with the SSRI sertraline or a placebo. Sixty-four percent of participants were male, with a mean age of 57 years.

The primary outcome was change in left ventricular ejection fraction, more than 5% being considered significant. The ejection fraction is the percentage of the ventricular diastolic volume which is pumped out during systole and is usually more than 65% in normal individuals. A reduced ejection fraction is the best measure of left ventricular dysfunction and a strong predictor of a poor outcome following an acute coronary syndrome. A level below 35% is particularly significant. Other outcomes, such as the number of recorded adverse cardiovascular events and measures of depression were also included. Depressive symptoms were assessed with the BDI and depressive disorders by the Diagnostic Interview Schedule.

At the end of the study period there were no statistically significant differences between the sizes of the left ventricular ejection fractions in the group who had received sertraline [baseline: 54%, at week 16: 54%]

compared with the control group receiving the placebo [baseline: 52%, at week 16: 53%]. However, the sertraline group reported a non-significant trend, approximately 20% less, towards fewer major cardiovascular events such as orthostatic hypotension or conduction abnormalities. Sertraline was found to be superior to placebo in its antidepressant efficacy for the patients with recurrent depressive disorders who had experienced an acute coronary syndrome, but not for the patients whose depression had first occurred at the time of their coronary event. However, there were two main limitations with this study. Firstly, the sample size was small. It was estimated that 4,000 patients would need to be recruited to reveal rarer adverse reactions. Secondly, treatment was not initiated until 34 days post event being the time it took for the participants to undergo a necessary range of safety screens before commencing treatment.

There has been a widespread use of SSRIs since the publication of the SADHART study. Other SSRIs such as fluoxetine, paroxetine and citalopram have all been studied although sertraline is the only SSRI not to carry a cautionary warning for use in cardiac patients.

Recently the use of various SSRIs preoperatively (Xiong et al 2006) in patients undergoing coronary revascularisation in the United States has led to higher incidences of rehospitalisation and increased mortality when compared to patients not taking SSRIs. This prospective study examined the long term outcomes of 5.1% [246] of a cohort of 4,548 pre-surgical coronary



patients who were taking SSRIs at the time of joining the study, between 1999 and 2003. The SSRIs examined in this study included fluoxetine, paroxetine, citalopram, and sertraline. Patients were followed up initially at 6 months and then annually with a self-report questionnaire for up to six years. The drop out rate from the study was 5%. Depression levels were not measured at any time during the study. The control group were the patients not taking the SSRIs. At baseline, the group on SSRI therapy had greater co-morbid illness with evidence of peripheral vascular disease, previous coronary interventions and diabetes. At the end of the follow-up period the group taking SSRIs pre-surgically was shown to have increased risks for mortality [HR 1.61, 95% CI 1.17,2.21] ( $p=0.003$ ) and also for re-hospitalisation, [HR 1.52 95% CI 1.30,1.77] ( $p<0.0001$ ) compared to those not taking SSRIs. However, patients requiring SSRIs because they are depressed are at greater risk anyway, so it is not clear whether SSRIs add that risk or not.

This study has several limitations. Firstly, the proportion of patients being treated with SSRIs at baseline was low at 5.1%. Other researchers have reported rates of around 20% in similar patients (Connerney et al 2001). Secondly, it was estimated that a further 2.7% of participants were taking other antidepressant medications, but rather than exclude these patients, they formed part of the control group, which may have biased the results obtained. Finally, depression levels were not assessed at any time during the study period, therefore it was not possible to ascertain whether any

crossover between the groups occurred in terms of increase or reduction in depressive symptoms or disorders or use of SSRIs, which may also have confounded the results.

A study has been published recently (van Melle et al 2007) which recruited 331 participants diagnosed with depression using ICD-10 criteria, from a cohort of 2177 myocardial infarction survivors. This multicentre randomised controlled trial aimed to compare the effectiveness of antidepressant treatments with usual care, using a variety of modalities. The study participants were assessed with the BDI during their hospital stay and 3, 6, 9 and 12 months after the acute event. Those found to be depressed whilst in hospital were also assessed with a structured interview, after 3 months had elapsed. The researchers delayed the structured interviews for several months to allow for the spontaneous recovery from depression during early convalescence. Outcome measures were the presence of continued depression and further cardiovascular events occurring over the follow up period of 18 months. Patients who were at significant risk for committing suicide were excluded, as were patients who had diseases likely to unfavourably influence short term survival and those already being treated for depression. Co-morbidity was reported using a modified version of the Charlson Comorbidity Index (Charlson et al 1987). The researchers accounted for the severity of coronary disease amongst participants using a variety of risk stratification tools such as Killip class and measurements of left ventricular ejection fractions.

Treatment for depression for the intervention group [n=209] consisted of several options:

1. A double-blind placebo controlled treatment of mirtazapine with or without the addition of an SSRI [citalopram] for those who did not respond to the mirtazapine
2. Pharmacotherapy or psychotherapy at the discretion of a psychiatrist with or without a referral to CR
3. No treatment

The group randomised to usual care [n=122] were offered a variety of treatments such as pharmacotherapy and psychotherapy which were provided at the discretion of local clinicians, or did not receive any treatment.

At baseline three-quarters of participants were male, with a mean age of 58 years. Most participants in the intervention group received treatment for depression. This was in contrast to the usual care group of whom only 7% had recorded evidence of treatment with antidepressant pharmacotherapy and 10% received non-pharmacological treatment.

At the end of the study period 66% of the cohort were assessed for long term depression. Forty percent were from the intervention group and 26% from the group who had usual care. There were no differences between the intervention and usual care group in either mean scores from the BDI



assessments [ $11.0 \pm 7.5$  versus  $10.2 \pm 5.1$  ( $p=0.45$ )], the presence of depressive symptoms using the ICD-10 criteria for diagnosis [30.5% versus 32.1% ( $p=0.68$ )] or the occurrence of cardiovascular events [OR 1.07, 95% CI 0.57,2.00]. One limitation of the study was its focus on a variety of modalities for treating depression, which may have reduced the power of the results obtained. Although not all patients in the intervention group were offered antidepressant medication as treatment, when the researchers performed a secondary analysis comparing patients who had received treatment with those who had not, they were still unable to detect a difference in the incidence of cardiovascular events between the two groups.

This study therefore did not provide evidence that treating depression improved either long term depression status or coronary outcomes over the 18 month follow-up period.

## ***7.2 Psychological interventions for coronary heart disease – The Cochrane Review***

Exercise therapy and counselling interventions are also widely used in the treatment of patients who suffer from both depression and coronary heart disease. However, until recently, little has been known about the effect of psychological interventions for depressed coronary heart disease patients. In the original Cochrane Review on comprehensive CR there were only four studies that had used validated questionnaires to assess depressive symptoms. As a result the researchers were unable to perform analyses or

report on the effectiveness of the psychological components in CR. However, a later systematic review by the Cochrane Collaboration (Rees et al 2004) has focused specifically on the effectiveness of psychological interventions and stress management training in coronary heart disease and summarises this evidence from the randomised controlled trials that were published up to December 2001. Therefore, I did not go back to the original cohort studies for this part of my review.

The studies in the Cochrane Review met the following criteria for inclusion: they were randomised controlled trials of non-pharmacological psychological interventions for participants who had been diagnosed with coronary heart disease and they had a minimum follow-up period of 6 months. Clinically qualified personnel delivered the interventions. These included single interventions, such as stress management or psychological interventions incorporated within comprehensive CR. The primary outcome measures were all-cause and coronary-related mortality, nonfatal coronary events, anxiety and depression. Using these criteria, the researchers identified 36 trials for inclusion, involving a total of 12,841 patients. Eleven of the trials had assessed depression, with a variety of different instruments. Results from these studies showed a significant reduction in depression for treated patients, with a standard mean difference of -0.3 [95% CI -0.48,-0.13]. The reviewers commented that the quality of many of the trials that were included was poor. The combined results from all the trials failed to show any effect from psychological interventions on mortality. Although a small reduction in



the incidence of nonfatal re-infarctions for the patients who had received either comprehensive CR or stress management, [OR 0.78 (0.67,0.90)] was reported, this was not seen in the two largest studies (Blumenthal et al 2004; Jones and West 1996) which between them had recruited over a third of the total number of participants.

The first of the larger studies evaluated psychological CR in England and Wales (Jones and West 1996). Six hospitals enrolled 2,328 patients (73% males), of all ages with an acute myocardial infarction. The exclusion criteria were a stay in hospital of over 28 days or being discharged to long-stay or institutionalised care. Patients were randomised to an intervention group who received psychological therapy, consisting of seven 2-hour sessions of group or individual counselling. The control group had a normal cardiology follow-up, but none of the usual components of comprehensive CR such as weight management, dietary and stop smoking advice and supervised or home exercise programmes. Outcome measures were total mortality, cardiovascular mortality, revascularisation, nonfatal myocardial infarction and measures of anxiety and depression. Depression was assessed by administration of the DSSI/sAD [Delusions-Symptoms-States Inventory/ states of Anxiety and Depression] within a semi-structured interview at baseline and at 6 months to assess psychological parameters. Participants were assessed by a second interview at 6 months in their homes, and at 12 months in the hospital outpatient departments. Outcome measures were



total mortality, cardiovascular mortality, revascularisation, nonfatal myocardial infarction and measures of anxiety and depression.

Seventy-three percent of participants attended the rehabilitation course. The drop out rate from the study was 6%. At baseline entry to the trial there were no differences between the intervention and control groups by age or HADS scores. Nineteen percent of participants in both groups had symptoms suggestive of depression at baseline, and this percentage remained the same at the 6-month assessment. There were no differences reported in changes in depression scores between the start and end of CR. At the end of the study period 7% of the cohort had died. The researchers were unable to show any statistical differences between the 2 groups in terms of either clinical outcomes or mortality.

There are several possible explanations for the null effect obtained from psychologically based CR in this study. Firstly, one in four of patients had declined to take part in the study due to transport difficulties and an ambulance strike. Therefore the final selection of patients enrolled into the study did not necessarily represent the total number of patients who were eligible. Secondly, the educational programmes attended by the patients were of short duration only. CR programmes are usually considered to last between 8-12 weeks in the United Kingdom and far longer in most of the studies published from North America. This could have affected the intensity of all the interventions and consequently the outcomes. Thirdly, the second

and final psychological assessment at 6 months post event may not have allowed sufficient time for the psychological treatment to show an effect or conversely any effect produced during the seven weeks of CR may have worn off by then. Finally, it was unclear whether members of the control groups had taken up exercise during the period of study, which could also have biased findings towards the null.

The only other large study from the Cochrane Review followed up myocardial infarction survivors by using a subset of depressed participants from the Enhancing Recovery in Coronary Heart Disease [ENRICHD] randomised controlled trial whom they reviewed at six months post event (Blumenthal et al 2004). There were 2,078 participants [43.5% females] with a mean age of 61 years who entered the study following an assessment for the continued presence of depression or a reported perception of having low social support. Depressive disorder was measured with the Depression Interview and Structured Hamilton [DISH] (Freedland et al 2002). The DISH consists of a semi-structured interview divided into 3 sections, with open ended questions, a section on current depression symptoms and a third part on psychiatric history. Depressive symptoms were assessed with the BDI. Exclusion criteria included the presence of major psychiatric co-morbidity, patients who were thought to be too ill to take part in the study, patients who had possible fatal non-cardiac conditions, patients who had undergone revascularisation procedures, and failure of patients to be enrolled into the study within a 28 day period of the acute event. Physical activity was self-reported by use of a



single item on an activity questionnaire. The D'Hoore Co-morbidity Index (D'Hoore et al 1993) was used to account for non cardiac and non-psychiatric co-morbid illness. Participants were randomly assigned to cognitive behavioural therapy sessions that were held in groups, or provided on an individual basis, or to usual care with all participants being given the opportunity to attend CR as part of routine care. Outcome measures included self-reported physical activity, depression, all-cause mortality and cardiovascular morbidity. Depressive symptoms and data on exercise habits were assessed after 6 months and then annually for up to four years.

During the four-year follow-up period, 9% of the cohort had died. Results indicated several differences between the participants who were exercisers and the non-exercisers in the uptake of treatments and lifestyle changes. Forty-two percent of exercisers had participated in cognitive behavioural therapy compared to 28% of non-exercisers. Forty-two percent of exercisers also attended CR compared to 13% of non-exercisers. Exercisers were less likely to be smokers [16% versus 23%] and to have modified their diets [57% versus 78%].

Survival analyses using a Cox proportional hazard model were performed using a variety of covariates which included smoking habit, co-morbidity, baseline depression level, change in depression level and cognitive behavioural therapy. The results demonstrated the importance of exercise training in reducing mortality in myocardial infarction survivors who were



either depressed or who had reported low levels of social support over an average follow-up period of two years. However, attendance at cognitive behavioural therapy sessions was not shown to be significant in any of the regression models.

There were twice as many deaths (12%) and a greater number of nonfatal myocardial infarctions (10.5%) in the non exercisers compared with the group who were still exercising regularly at the final follow-up (5.7%, 6.5% respectively). The adjusted HR was 0.62, [95% CI 0.44,0.86 ( $p=0.004$ )] for fatal events and 0.72, [95% CI 0.52,0.99 ( $p=0.044$ )] for nonfatal myocardial infarction. The regular exercisers had lower depression scores ( $p=0.0004$ ) at the start of the study, and a significantly greater decrease from baseline depression scores ( $p < 0.0001$ ). However, the effect of self-reported physical activity on baseline depression levels and changes in depression scores over time was not significant ( $p=0.672$  and  $p=0.819$  respectively).

There were several weaknesses with the design of this study. The patients had only one opportunity during the 6-month period to recall and self-report on their exercise habit. There was no way of distinguishing whether those who said they were exercisers were exercising because they were less depressed or whether they were less depressed because they had become regular exercisers. A further limitation was the lack of clarity concerning the concept of self-reported 'exercise'. The patients were a self-selected group in terms of self-report of exercise behaviour, with only some of those, who

professed to be exercisers having had access to CR programmes. Five hundred and fifty-four patients from the original ENRICHD cohort had attended certain components of CR, of which less than half had participated in supervised exercise-based CR. It is difficult to compare these results with other CR studies because the timing of the psychological assessments at 6 months was later than usually reported in CR studies. The results from this study, therefore, can only be generalised to myocardial infarction survivors who are either lacking in perceived social support, suffering from a form of depression or both.

### ***7.3 Observational studies of exercise and depression in coronary heart disease***

Although some studies have been performed which looked at the effect of exercise as a treatment for depression in coronary heart disease, few have followed up participants in the long term or reported on mortality as a primary end point. However, I found one observational study (Milani et al 1996) which although it did not collect survival data on participants, did examine the efficacy of exercise therapy in a group of 338 coronary heart disease patients [22% female] with elevated depression scores. The patients were enrolled into the study whilst participating in a CR programme. They had either been in hospital with a myocardial infarction or undergone coronary revascularisation 4-6 weeks prior to the start of the study. All participants were less than 76 years of age. Those taking antidepressant medication or lipid lowering drugs were excluded from participation. Depressive symptoms



were assessed with a validated, self-report questionnaire (Kellner 1987). The participants' cardiorespiratory fitness levels were measured by treadmill exercise testing prior to enrolment in an exercise and educational CR programme. The CR programme required participants to attend 3 times a week for 12 weeks. Fitness and psychological outcomes were reassessed at the end of the 3-month period.

The researchers categorised depression scores into moderate or severe. At baseline 69 [20%] of the cohort was found to be depressed with just over one-half of this group reporting symptoms of severe depression. The depressed group was also younger ( $p=0.06$ ), reported to be heavier smokers ( $p=0.07$ ) and less fit ( $p=0.01$ ) when compared to the non-depressed group. By the end of the CR programme the percentage of depressed patients had fallen significantly to 6.8%, of which 4.14% reported symptoms of severe depression and 2.66% symptoms of moderate depression ( $p<0.0001$ ). The change in depression scores was significant in the depressed group between the start and completion of CR. ( $p<0.0001$ ). However, 6% of participants from the non-depressed group had developed depressive symptoms by the end of CR.

Exercise capacity was also shown to improve in both depressed and non-depressed participants ( $p<0.001$ ). In depressed participants before CR mean exercise capacity was  $4.9 \pm 2.1$  METS which rose to  $7.4 \pm 3.5$  by the end of the programme ( $p<0.001$ ) and translated into a 51% improvement in



fitness. This compared with a mean exercise capacity in the non-depressed group of  $5.8 \pm 2.4$  at the start of CR and  $7.9 \pm 3.6$  at the end of the Phase III programme ( $p < 0.001$ ). For the non-depressed group this represented a 36% change in exercise capacity

This study showed that attending 36 sessions of formal educational and exercise-based CR increased fitness levels and reduced symptoms of depression in depressed coronary heart disease participants who joined a CR programme within 6 weeks of their index event or procedure.

There were several limitations with this study. The study participants were a self-selected group who had previously consented to join a CR programme. They may therefore not be representative of all coronary heart disease patients. It is also not clear how specific or sensitive The Symptom Questionnaire (Kellner 1987) is at detecting symptoms of depression in coronary patients, although it has been extensively validated and used to measure psychological symptoms in heart-lung patients. I was unable to find any other studies in the coronary population that had used this questionnaire to assess depression. Finally, the follow-up period for this study was short and it was not known whether the immediate beneficial effects of CR would endure over the passage of time.

## **7.4 Summary**

Depression is gaining recognition as a risk factor in coronary heart disease progression and therefore treatment for depressive symptoms or disorders may be of prognostic importance. The choice of antidepressant medication is also important as many antidepressants have a potential for provoking adverse cardiovascular side effects. Results from recent studies indicate that the SSRIs are safer than tricyclic antidepressants for treating depression in people with coronary disease. SSRIs versus placebo have been found to be effective in treating patients with a prior history of depressive disorder and recent myocardial infarction or unstable angina, and have also been shown to be less likely to provoke cardiovascular events effects (Glassman et al 2002). Sertraline appears to be the SSRI of choice and is recommended by NICE<sup>i</sup> for use in myocardial infarction patients or patients with unstable angina.

However, a recent study which used a variety of modalities including pharmacotherapy and psychotherapy to treat depressed myocardial infarction survivors, was unable to provide evidence that treating depression at the time of the event improves either depression status or coronary outcomes (van Melle et al 2007). Future research needs to explore the role of all antidepressant treatments, including pharmacotherapy and psychotherapy and their effects in a wide range of coronary heart disease patients, as long term data is limited.

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<sup>i</sup> NICE The National Institute for Clinical Excellence Guideline

The effectiveness of psychosocial interventions in the treatment of coronary heart disease remains unclear, as the two largest studies were unable to show the beneficial effect from either psychological or cognitive behavioural therapies (Jones and West 1996; Blumenthal et al 2004). The Cochrane reviewers concluded that although psychological interventions did appear to alleviate levels of depression, the overall effect of any treatment was small. It has been suggested that further research in this area should be directed towards explicit psychological interventions for patients attending CR programmes which take into account four factors: the timing and duration of interventions, the expertise of those that provide them, and the co-morbid state of the patients receiving them (Stokes 2004).

The study by Milani et al (1996) is the only one of which I am aware that focused specifically on the role of exercise therapy in treating depressed coronary patients and which reported changes of fitness and depression levels as outcome measures at the end of a CR programme. The important finding from this study was that depressed patients showed greater gains in fitness when attending CR compared with those who were not depressed. The depressed patients improved their exercise capacity by 51% compared with the gain of 36% for the non depressed patients. There may be many reasons that contribute to this benefit. Unfortunately, this study did not report survival data as this may have helped to clarify the effects of physical training for depressed coronary patients in the longer term.



## Chapter 7: References

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# **Chapter 8**

## **Methodological Issues**

### ***8.1 Using a cardiac rehabilitation cohort for research***

Not all cardiac patients have access to rehabilitation and many are denied the opportunity to attend a supervised programme. CR appears to be offered to a minority of patients who might benefit (Bethell et al 2001; Lewin et al 1998; Thomas et al 1996) and a significant number who are recruited for rehabilitation, fail to complete their programme (Bethell et al 1999). In England, for instance, of 131,089 eligible cardiac patients in 2000, 45-67% were referred to rehabilitation but only 27-41% actually attended (Griebsch et al 2004). The situation is similar in North America where a recently published longitudinal survey of patients found that approximately half of heart attack survivors were participants in rehabilitation in Minnesota during the 16 year timeframe of surveillance and that women and the elderly, independently of other characteristics were less likely to enrol (Witt et al 2004).

In a study performed in our programme we found that non-compliance with CR was an important risk factor for a poor prognosis (Turner et al 2002). The ability to predict which patients were least likely to comply with CR would be useful and enable health professionals to focus more effort on such patients to encourage their long-term adherence to healthy lifestyle changes.



A number of different factors are related to whether a patient starts the CR programme and then persists with it. An important factor is whether the patient volunteers for CR or is automatically referred. Patients are more likely to enrol in CR if encouraged to do so by the cardiologist in charge of their care (Horgan et al 1992). One of the milestones for CR in The National Service Framework for Coronary Heart Disease (DOH 2000) is to offer CR to 85% of patients following acute myocardial infarction or after revascularisation.

There is often poor uptake amongst women, ethnic minority groups, those patients at high risk of further cardiac problems and the elderly. Many researchers have reported that there is a greater likelihood of any of these patients dropping out of the programme prior to completion of an exercise-based rehabilitation course (Evenson and Fleury 2000; McGee and Horgan 1992; Pell et al 1996; Romeo and Saccucci 1991; Thow et al 2000).

The rate of non-completion from short term CR programmes reported over the past 30 years is similar to the rate we have reported previously from our programme; ranging from 14-20% (Carson et al 1982; Gutin et al 1990; Turner et al 2002; Williams et al 1985). It has been suggested that those who have the most to gain from rehabilitation are the least likely to be enrolled, and are the most likely to fail to attend the CR course (Harlan et al 1995; Oldridge et al 1978). For instance, non-compliance with CR is greatest

amongst inactive smokers who had already suffered a previous myocardial infarction (Oldridge et al 1978). Compliance is also affected by age (Evenson et al 1998; Pell et al 1996) and gender, with a higher dropout rate being observed in females and in the elderly (McGee and Horgan 1992; Moore et al 1998; Thow 2000), whilst others have found that the presence of anginal symptoms is a significant predictor of non-completion of CR (Oldridge et al 1983; van Dixhoorn et al 1990).

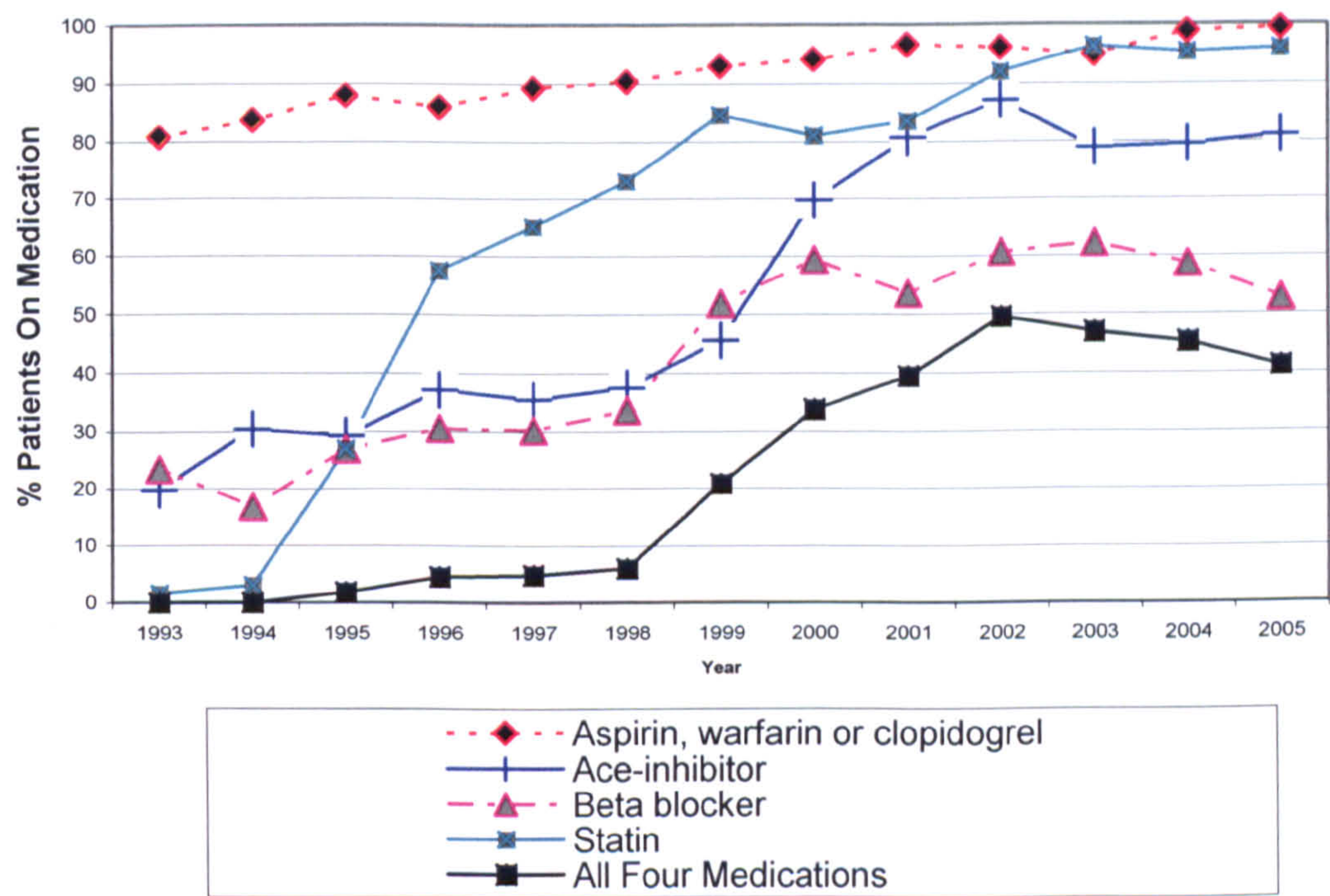
All of this means that a cohort of CR patients such as the one in this study may not be representative of people with coronary disease as a whole.

## ***8.2 Developments in coronary heart disease secondary prevention measures***

Secondary prevention for coronary patients has changed over the last 15 years. The prognosis of the patients diagnosed with coronary heart disease has improved as new treatments and interventions such as thrombolysis have become available. It is inevitable that during the course of recruitment to CR some of the patients in this study were exposed to more effective treatment and in particular to more effective drug therapies [Figure 8:1].



**Figure 8:1 Changes in use of secondary prevention medication at the Basingstoke & Alton Cardiac Rehabilitation Programme between 1993 and 2005**



For example, the introduction of the routine use of statins was the first evidence-based therapy to help limit coronary disease progression (Bowles et al 2004). Government targets have encouraged use of all medications that are effective in reducing coronary heart disease progression, namely statins, aspirin,  $\beta$  blockers and, more recently, ace inhibitors. The evidence base for this combination of medication is well-established (Borg 1967; Ho et al 2004; Veverka and Jolly 2004) although not necessarily being met (Lawlor et al 2004). Lower targets for blood pressure levels to control hypertension have also lead to an increased use of cardiovascular drugs.

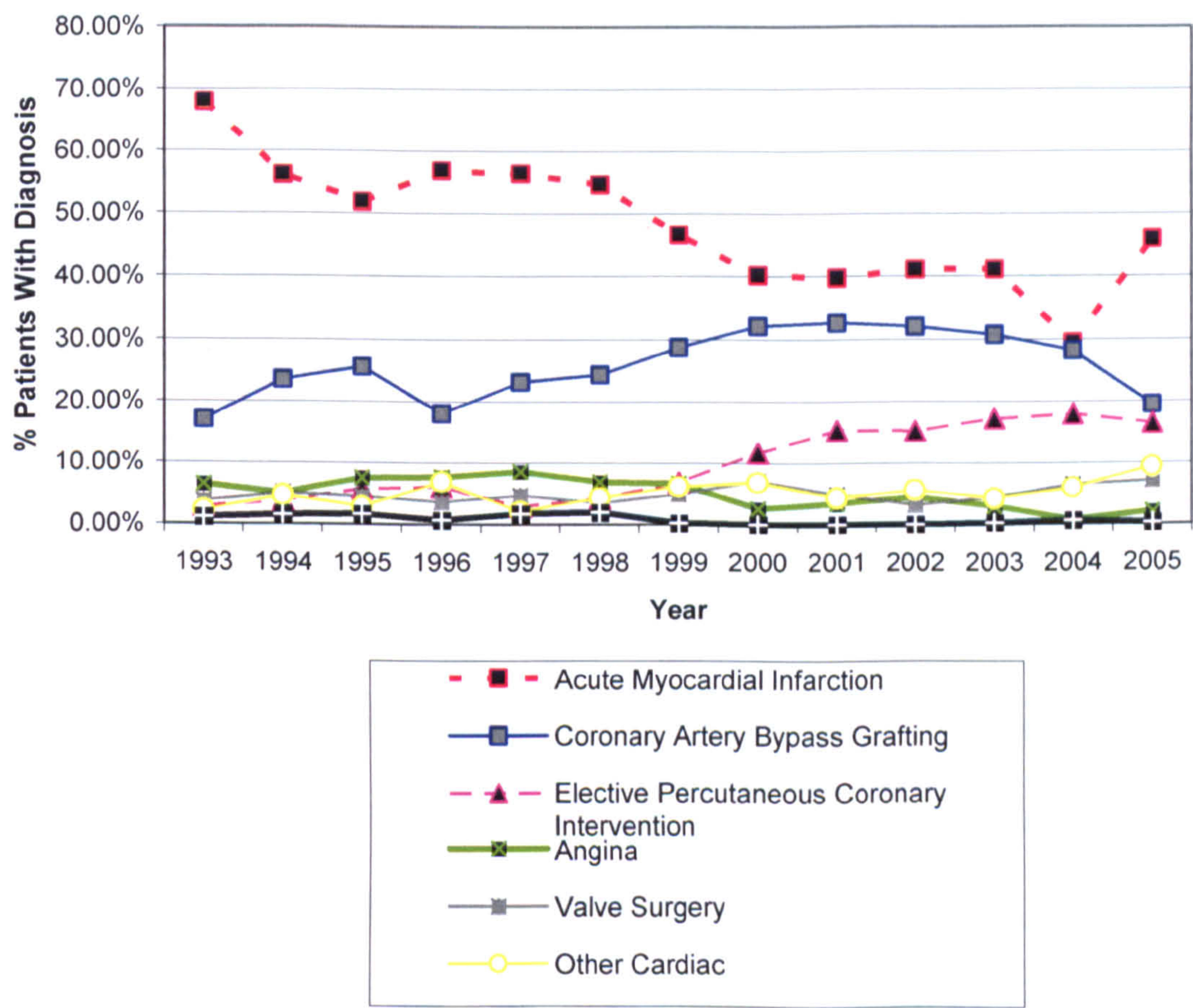


As well as the new drug therapies that have become available there were several other important changes in the management of patients during the study period. In 1998 the Basingstoke and North Hampshire Foundation Trust appointed its first interventional consultant cardiologist, who was joined by a second consultant three years later. With the increase in the use of percutaneous coronary intervention procedures there has been a reduction in bypass grafting but a significant increase in the number of patients enrolled in our programme [Figure 8:2].

Furthermore, there have been recent changes in the way a diagnosis of myocardial infarction or coronary heart disease is made and there are new types of revascularisation procedures available, as I discussed in Chapter 2. Such innovations require changes in the organisation of CR to accommodate a greater volume of patients with different requirements. We are seeing an increasing number of elderly patients, and a greater number of myocardial infarction patients who have undergone immediate primary or rescue angioplasties.



**Figure 8:2** Changes in diagnostic reasons for enrolment to the Basingstoke & Alton Cardiac Rehabilitation Programme between 1993 and 2005



### 8.3 Choice of variables to include in the analysis

#### 8.3.1 Measuring physical fitness

It has been possible to assess cardiorespiratory fitness for most of the coronary patients who participated in our CR programme. We used two methods to achieve this. Patients tested up to 9<sup>th</sup> August 1995 were assessed on a bicycle ergometer. A stepped protocol of 3-minute stages was used, with a starting level of 25 or 50 watts, increasing by 25 watts per stage. The end point was taken at a perceived exertion rating 6 or 7 out of a



range of 1-10 (Borg 1967), unless the test had been stopped by angina, arrhythmia, hypotension or maximum heart rate. Peak  $\text{VO}_2$  was thus predicted from the known oxygen cost of cycling at the final workload attained and divided by the weight of the patient to give a figure in ml/kg/min.

We acquired an exercise treadmill with an electrocardiograph facility at the beginning of August 1995. From 10<sup>th</sup> August that year most new patients were assessed on the treadmill with a few exceptions for those who could not walk on the treadmill, but could bicycle, usually because they had orthopaedic limitations. The Bruce protocol [full Bruce] (Bruce et al 1973) was used for most patients, but a modified version [modified Bruce protocol] was used for patients whose age and physical condition made it unlikely that they would be able to perform at least 3 minutes of the full Bruce protocol [Table 8:1]. For the full Bruce protocol, oxygen uptake was estimated as 3.5ml/kg/min for each full minute performed added to the basal rate of 3.5ml/kg/min. For the modified Bruce protocol, oxygen uptake was estimated as 3.5ml for each 3-minute stage for the first 3 stages. At the end of the exercise programme, everyone who completed the programme was retested using the same method and protocol as was used for the initial test. Chapter 9 includes a description of the protocols we used for exercise testing and explains how the data collection was achieved.



**Table 8:1 Modified and Full Bruce Protocol**

STAGE		SPEED (MPH)	GRADE %	DURATION (mins)	METS
Modified Bruce	Full Bruce				
1	-	1.7	0	3	1.7
2	-	1.7	5	3	2.9
3	1	1.7	10	3	4.7
4	2	2.5	12	3	7.1
5	3	3.4	14	3	10.2
6	4	4.2	16	3	13.5
7	5	5.0	18	3	17.3

Adapted from 'Principles in Exercise Testing by R.A.Bruce, 1973

**8.3.2 Measuring depression and psychological state**

There are two main ways of assessing psychological state, by standardised clinical interviews and by self-report questionnaires. A combination of the two methods may be used, as for example in the ENRICHD trial (Blumenthal et al 2004). Each method of assessment has its own merits and the choice of technique may depend upon factors such as the type of detailed information that is required, the funds available for a project, the sample size, or the location of the research.

Standardised clinical interviews may be subdivided into those carried out during epidemiological research or probing, in-depth interviews. Lay interviewers often conduct the former by reading out standard questions to the interviewees and recording their answers. Health professionals, who are

required to undergo special training in interviewing skills, carry out probing or in-depth interviews.

In contrast, standardised self-report questionnaires can be easily completed during a clinical appointment, or by post or emails, as a part of patient assessment. Using this method it is possible to detect depressive symptoms, and to differentiate between symptoms suggestive of clinical depression and non-depressed states. Self-report questionnaires have several advantages over interview techniques. They are quick and cheap to administer, easy to score and analyse and give instant results. This was the main reason for selecting this type of instrument for regular use in our CR programme. There are many psychosocial assessment instruments for CR patients in use and there is no general agreement as to which instruments are the most helpful and which should be used routinely to ascertain changes in psychosocial status during CR (McGee et al 1999). This is an on-going problem for those of us measuring the psychological state of our CR patients.

Interpretation of results is often complicated. The availability of a wide range of instruments means it is difficult to compare individual study results, when different instruments have been used to measure similar things. The timing of assessments also varies between studies. For instance, in research carried out specifically on coronary heart disease patients, some researchers measure depression in hospital (Lewin et al 1992), whilst others do so at

about one month post event (Mayou et al 2002), or, as we did, at the start of Phase III, which is about 4-5 weeks after the event.

The most common questionnaire used to assess psychological state in CR in the United Kingdom (Bethell et al 2004) is the HADS (Zigmond and Snaith 1983). It was designed initially to detect emotional disorders and was used in medical outpatient clinics but not necessarily in people with coronary disease. It has since been shown to be an acceptable, reliable and valid measure with sensitivities and specificities of more than 80% for detecting anxiety and depression in physical illness (Herrmann 1997). The BDI is another popular instrument available for measuring depression and is also widely used in research in coronary heart disease (Beck et al 1961). It is the most commonly used instrument for measuring depression in the general population in the United Kingdom (Bradford 2005) and has been used in widely in studies involving people with coronary disease (Blumenthal et al 2004; Carney et al 2001; Connerney et al 2001). The BDI consists of 21 items and is, like the HADS, easy to administer and score. However, in the United Kingdom the majority of CR programmes measuring psychological state use the HADS as recommended by national CR guidelines (Coats et al 1995) and the National Service Framework for Coronary Heart Disease (DOH 2000). In a survey performed by the BACR/BHF, 52 CR programmes, out of the 302, measured the psychological state of their coronary patients. Eighty-eight per cent of these programmes were found to be using the HADS



(Bethell et al 2000), possibly because the BDI has to be purchased by users, while the HADS is a free resource (Bethell et al 2000).

The HADS consists of 14 questions divided into two subscales, each of which includes four possible responses, which are presented in a tick box format. The patient is asked to rate each question and tick the box they judge best to correspond with their current state of mind. The questions, which are weighted 0–3, alternate between measuring traits of either anxiety or depression. The minimum score for either trait is zero and the maximum 21. The clinician adds up the weighted scores separately for the two domains, the greater the anxiety or depression, the higher is the score. A score of between 8 and 10 indicates borderline anxiety or borderline depressive symptoms and above 10 suggests symptoms of clinical anxiety or depression. The HADS is easy to apply and rapidly interpreted by clinicians. As seen in Figure 8:3, the numbers in the boxes refer to the weighting of each answer; these are masked on the patient's form.



Figure 8:3 HAD Scale – Questions and Scoring

**Instructions:** Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

<b>I feel tense or 'wound up':</b>	<b>A</b>	<b>I feel as if I am slowed down:</b>	<b>D</b>
Most of the time	<input type="checkbox"/> 3	Nearly all of the time	<input type="checkbox"/> 3
A lot of the time	<input type="checkbox"/> 2	Very often	<input type="checkbox"/> 2
Time to time, occasionally	<input type="checkbox"/> 1	Sometimes	<input type="checkbox"/> 1
Not at all	<input type="checkbox"/> 0	Not at all	<input type="checkbox"/> 0
<b>I still enjoy the things I used to enjoy:</b>	<b>D</b>	<b>I get a sort of frightened feeling like 'butterflies in the stomach':</b>	<b>A</b>
Definitely as much	<input type="checkbox"/> 0	Not at all	<input type="checkbox"/> 0
Not quite so much	<input type="checkbox"/> 1	Occasionally	<input type="checkbox"/> 1
Only a little	<input type="checkbox"/> 2	Quite often	<input type="checkbox"/> 2
Not at all	<input type="checkbox"/> 3	Very often	<input type="checkbox"/> 3
<b>I get a sort of frightened feeling like something awful is about to happen:</b>	<b>A</b>	<b>I have lost interest in my appearance:</b>	<b>D</b>
Very definitely and quite badly	<input type="checkbox"/> 3	Definitely	<input type="checkbox"/> 3
Yes, but not too badly	<input type="checkbox"/> 2	I don't take as much care as I should	<input type="checkbox"/> 2
A little, but it doesn't worry me	<input type="checkbox"/> 1	I may not take quite as much care	<input type="checkbox"/> 1
Not at all	<input type="checkbox"/> 0	I take just as much care as ever	<input type="checkbox"/> 0
<b>I can laugh and see the funny side of things:</b>	<b>D</b>	<b>I feel restless as if I have to be on the move:</b>	<b>A</b>
As much as I always could	<input type="checkbox"/> 0	Very much indeed	<input type="checkbox"/> 3
Not quite so much now	<input type="checkbox"/> 1	Quite a lot	<input type="checkbox"/> 2
Definitely not so much now	<input type="checkbox"/> 2	Not very much	<input type="checkbox"/> 1
Not at all	<input type="checkbox"/> 3	Not at all	<input type="checkbox"/> 0
<b>Worrying thoughts go through my mind:</b>	<b>A</b>	<b>I look forward with enjoyment to things:</b>	<b>D</b>
A great deal of the time	<input type="checkbox"/> 3	As much as I ever did	<input type="checkbox"/> 0
A lot of the time	<input type="checkbox"/> 2	Rather less than I used to	<input type="checkbox"/> 1
From time to time but not too often	<input type="checkbox"/> 1	Definitely less than I used to	<input type="checkbox"/> 2
Only occasionally	<input type="checkbox"/> 0	Hardly at all	<input type="checkbox"/> 3



<b>I feel cheerful:</b>	<b>D</b>	<b>I get sudden feelings of panic:</b>	<b>A</b>				
Not at all	<table border="1"><tr><td>3</td><td></td></tr></table>	3		Very often indeed	<table border="1"><tr><td></td><td>3</td></tr></table>		3
3							
	3						
Not often	<table border="1"><tr><td>2</td><td></td></tr></table>	2		Quite often	<table border="1"><tr><td></td><td>2</td></tr></table>		2
2							
	2						
Sometimes	<table border="1"><tr><td>1</td><td></td></tr></table>	1		Not very often	<table border="1"><tr><td></td><td>1</td></tr></table>		1
1							
	1						
Most of the time	<table border="1"><tr><td>0</td><td></td></tr></table>	0		Not at all	<table border="1"><tr><td></td><td>0</td></tr></table>		0
0							
	0						

<b>I can sit at ease and feel relaxed:</b>	<b>A</b>	<b>I can enjoy a good book or radio or TV programme:</b>	<b>D</b>				
Definitely	<table border="1"><tr><td></td><td>0</td></tr></table>		0	Often	<table border="1"><tr><td>0</td><td></td></tr></table>	0	
	0						
0							
Usually	<table border="1"><tr><td></td><td>1</td></tr></table>		1	Sometimes	<table border="1"><tr><td>1</td><td></td></tr></table>	1	
	1						
1							
Not often	<table border="1"><tr><td></td><td>2</td></tr></table>		2	Not often	<table border="1"><tr><td>2</td><td></td></tr></table>	2	
	2						
2							
Not at all	<table border="1"><tr><td></td><td>3</td></tr></table>		3	Very seldom	<table border="1"><tr><td>3</td><td></td></tr></table>	3	
	3						
3							

Several researchers have used the HADS to detect psychological distress in patients who have suffered a myocardial infarction (Barth et al 2004; Budde and Keck 2001; Kittel et al 2003; Martin et al 2003; Whitmarsh et al 2003), and Martin and colleagues have examined its performance at different stages of coronary illness. Martin’s research involved 335 myocardial infarction patients, who completed the questionnaire on three separate occasions: during their stay in the coronary care unit, at 6 weeks and at 6 months. The researchers tested the questionnaire for both internal and test-retest reliability, for total anxiety and depression scores, and also for scores within the subscales. Results from this study showed the HADS to be a reliable instrument for detecting psychological state in people with coronary disease.

### 8.3.3 Risk stratification

All patients who are recruited to exercise-based CR undergo risk stratification during initial assessment. Exercise testing is a part of this process. Risk stratification enables an appropriate and individualised exercise prescription



to be planned for patients that reflects the severity of cardiac illness, co-morbidity and current medical state. Each patient is assessed and categorised into one of three levels of risk of a further cardiac event: high, medium, or low. The American Association of Cardiovascular and Pulmonary Rehabilitation [AACVPR] [Figure 8:4] was the first to lay down criteria for risk stratification. The index of co-morbidity (Zoghbi et al 2004) that I have used in this research are based on these criteria. Current risk stratification of CR patients in the United Kingdom is based on similar criteria, and a mix of these criteria is widely recommended and used within the CR field in this country (AACVPR 1999; BACR 1997; SIGN 2002).

**Figure 8:4 Risk stratification criteria for cardiac patients (AACVPR 1999)**

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**LOW RISK**

Uncomplicated MI, CABG, angioplasty or atherectomy  
Functional capacity equal to or greater than 6 METS 3 or more weeks after clinical event  
No resting or exercise induced myocardial ischaemia manifested as angina and/or ST segment displacement  
No resting or exercise-induced complex arrhythmias  
No significant left ventricular dysfunction (Ejection fraction equal to or greater than 50%)

**MODERATE RISK**

Functional capacity less than 5- 6 METS 3 or more weeks after clinical event  
Mild to moderately depressed left ventricular function (Ejection fraction 31-49%)  
Failure to comply with exercise prescription  
Exercise induced ST-segment depression of 1-2mm or reversible ischaemia defects (echocardiography or nuclear radiography)

**HIGH RISK**

Severely depressed left ventricular function (Ejection fraction equal to or less than 30%)  
Complex ventricular arrhythmias at rest or appearing or increasing with exercise  
Decrease in systolic blood pressure of >15mmHg during exercise or failure to rise consistent with exercise workloads  
MI complicated by Congestive Heart Failure, cardiogenic shock and/or complex arrhythmias  
Patients with severe CHD and marked (>2mm) exercise induced ST-segment depression  
Survivor of a cardiac arrest

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The principle factors for deciding the risk each patient carries are as follows:

1. The extent of cardiac muscle damage, causing ventricular dysfunction especially of the left ventricle
2. The presence of residual ischaemia indicating persisting coronary narrowing
3. The provocation of ventricular arrhythmias by exercise.

Other features of risk stratification for consideration are a history of:

1. an infarction over the anterior surface of the heart muscle (which is generally larger and involves the left as opposed to the right ventricle) rather than an inferior infarction, involving the smaller right ventricle
2. more than one previous infarction
3. high cardiac enzyme levels at the time of infarction suggestive of greater areas of damage to the myocardium/heart muscle
4. complications such as left ventricular failure or cardiogenic shock
5. symptoms such as severe breathlessness due to exertion and orthopnea (breathlessness when lying down, which can only be relieved by sitting upright)
6. the finding of a large heart or pulmonary venous congestion on the chest X-ray and of a low ejection fraction on the echocardiogram
7. a low capacity on an exercise treadmill test, with significant electrocardiographic changes



8. a poor heart rate and blood pressure response, for instance heart rate rises very rapidly or systolic blood pressure falls with incremental exercise which indicates a poor left ventricle
9. the presence of current angina pectoris, and whether the pattern of the angina is predictable or not predictable.

Adapted from: (BACR 1997)

#### **8.3.4 Co-morbidity indices**

Any disease that is present, in addition to a primary diagnosis, may be referred to as a co-morbid condition. Co-morbidity is important to measure because it may be a confounding factor when assessing the risk of mortality. For instance, as well as having an initial diagnosis of coronary disease, a patient may be suffering from other medical conditions such as gout, diabetes, or a skin problem; all of which may be considered to be co-morbid illnesses. Moreover, a coronary patient with diabetes can suffer with co-morbid diabetic retinopathy or neuropathy. Co-morbid illnesses affect both function and survival. For this reason, several researchers have experimented with ways of accounting for co-morbidity by categorising and weighting certain diseases numerically so that a meaningful figure is obtained that relates to disease severity and survival, and is capable of inclusion into analyses. In my literature search I found three co-morbidity indices that are currently used in a variety of medical settings (Charlson et al 1987; D'Hoore et al 1996; Zoghbi et al 2004)

The Charlson Comorbidity Index is a validated tool for predicting short term and long term mortality from medical records (Charlson et al 1987). As it stands today, it consists of 19 categories of co-morbidity that were based on ICD-9 for a variety of medical conditions. Each code is weighted and based on an adjusted risk of one-year mortality. However, a recent update on the Charlson Index from the University of Manitoba (Burchill 2003) cautions users about its limitations; the codes in the programme refer to either complications or to co-morbidity diagnoses and, when applied, may result in an overestimation of co-morbid burden for certain diseases. Several researchers have validated the Charlson Index for use to predict mortality with coronary heart disease patients (D'Hoore et al 1993; Ghali et al 1996; Grace et al 2005; Roos et al 1989) and it has recently been used by Grace and colleagues in the study I discussed in Chapter 5. However the lower weightings assigned to certain diseases commonly seen in CR settings in the Charlson Index, such as peripheral vascular disease or myocardial infarction may to be inadequate and inappropriate (Ghali et al 1996). This is another problem when using this index to measure co-morbidity in CR programmes.

An adaptation of the Charlson Index has been developed by D'Hoore (D'Hoore et al 1996) which has the main advantage compared with previous versions of being simpler to use (Deyo et al 1992; Romano et al 1993) because it only uses the first 3 digits of the ICD-9 codes. This makes it easier to read and score and also provides a less complex approach to some of the diseases. For example it does not differentiate between



uncomplicated diabetes and diabetes that presents with complications. This makes it a more attractive tool to use in CR settings. It has been validated for use with coronary heart disease inpatients as the patients in the study used to develop the D'Hoore Index were coded for their co-morbidity during their inpatient stay.

A modification of D'Hoore's Index, The Modified D'Hoore Co-morbidity Index, [Table 8:2] has been developed specifically for use in CR programmes and avoids duplications of some of the weightings (Zoghbi et al 2004). This index was designed for assessing non-cardiac conditions specifically in the out-patient CR environment, as opposed to in the acute setting. It also acted as a supplement to the usual AACVPR risk stratification tool, which some researchers did not consider capable of accounting for the true burden of co-morbid illness in their coronary patients. Zoghbi et al omitted myocardial infarction and congestive heart failure from the index because these were already included in the AACVPR tool and would otherwise have been duplicated within the weightings. Leukaemia, lymphoma and tumours were combined into one category labelled malignancy and a diagnosis of hemiplegia was assigned a weight of 2 as opposed to other less disabling forms of cerebrovascular diseases such as transient ischaemic attacks, which were weighted as 1 [Table 8:2].

**Table 8:2 The Modified D’Hoore Co-morbidity Index**

Weight	Condition
1	Myocardial infarct* Congestive heart failure* Peripheral vascular disease Dementia Cerebrovascular disease† Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease‡
2	Hemiplegia‡ Moderate/severe renal disease (end stage) § Diabetes Any tumour# Leukaemia# Lymphoma#
3	Moderate or severe liver disease
6	Metastatic solid tumour

\*Myocardial infarct and congestive heart failure were omitted from the index because they are included in the AACVPR risk stratification for events.

†includes patients with history of stroke or history of cerebrovascular disease.

‡Mild liver disease and hemiplegia were omitted from index because it could not be quantified in Zoghbi database

§Includes patients with end stage renal disease

#Labelled as one category (malignancy)

Source:(Zoghbi et al 2004)

In Zoghbi’s study the 490 participants [mean age 60.1 ±11.6 years, 35.5% females,] were categorised into low, medium or high risk groups using the AACVPR risk stratification. A co-morbidity score was then computed for each participant.

The researchers found a high prevalence of co-morbidity in the study participants at baseline. About 40% of participants not classed as high risk using the AACVPR tool were classified as high risk by means of The Modified D’Hoore Co-morbidity Index computations. Logistic regression analysis, adjusted for age, race and gender showed that the AACVPR risk stratification process and the Modified D’Hoore Co-morbidity Index



independently predicted future cardiac events in the short term: AACVPR: [OR 1.56, 95% CI 1.14,2.12], Modified D'Hoore Co-morbidity Index: [OR 1.23, 95% CI 1.03,1.47] amongst study participants. However, prediction was better when both tools were used in combination.

I decided to allocate scores to the patients in my study using the Modified D'Hoore Co-morbidity Index for several reasons. Firstly, risk stratification of our patients took place at the start of the Phase III exercise component of CR, which was similar to the timings reported in Zoghbi's study. Secondly, we recorded coronary co-morbid illnesses, such as congestive cardiac failure and myocardial infarction, as Zoghbi had done, within the risk stratification process during the patient's initial Phase III assessment. Thirdly, because of the reduction in the number of categories of co-morbid illness and their weightings, scoring was less complicated than with either of the earlier indices. A limitation of the Modified D'Hoore Co-morbidity Index was that the long term predictive value of this index is unknown, as it has only recently been developed.

### **8.3.5 Indices of Deprivation**

Socio-economic deprivation is an important consideration in cardiovascular outcomes (Tunstall-Pedoe and Woodward 2006). The concept of linking deprivation indices to the health services was introduced to explain the socio-geographical variations that researchers found in uptake of services and

premature mortality. Deprivation measures have been devised over the past 35 years in an attempt to target health care and reduce health inequalities

Over time much has been done to improve the original measures as deprivation is considered to be “relatively dynamic in nature” (ODPM 2004). Over the past 20 years a variety of deprivation indices that linked specifically to Health Care have been developed. The Jarman and Townsend (Jarman 1991; Townsend et al 1985) and the Scottish Deprivation Score, known as Carstairs (Morris and Carstairs 1991) are most frequently used within the CR setting. Morris and Carstairs examined five indices including the three that focused on health care [Table 8:3].



**Table 8:3 Range of variables in any of the five deprivation indices**

	Scottish Deprivation or Carstairs	Jarman	Townsend	Department of the Environment	Scottish Development Department Index
Unemployment		x	x	x	x
Youth unemployment					x
No car	x		x		
Low social class	x				
Unskilled		x			x
Overcrowding	x	x	x	x	
Below occupancy norm					x
Not owner-occupied			x		
Lacking amenities				x	x
Single parent		x		x	x
Under age 5		x			
Elderly households					x
Lone pensioners		x		x	
1-year immigrants		x			
Ethnic minorities		x		x	
Vacant dwellings				x	
Level and access (old)				x	
Level and access (<5)				x	
Permanent sickness				x	
Large households				x	

Source: (Morris and Carstairs 1991)

The measure Morris and Carstairs used was found to correlate closely with standard mortality rates and was marginally superior to the Townsend score.

The Jarman index was devised for use in Primary Medical Care and focused on general practitioners' workload in order to ascertain resource allocation and is therefore not relevant for this research. The indices of Morris and Carstairs and Townsend were designed to score material deprivation. It is not clear how well either of these perform compared with the new indices that have been developed, although Morris and Carstairs has been used recently in research on socio-economic deprivation and post-operative cardiovascular outcomes (Taylor et al 2003).

The Indices of Multiple Deprivation [IMD] were introduced in 2000 (ODPM 2000) and updated in 2004 (ODPM 2004) and may be a more accurate way of scoring deprivation in this study because much of our catchment area lies in a rural, as opposed to urban, environment. Neither Townsend nor Carstairs accounted for rural deprivation (Jordon 2005). The new and revised IMD 2004 version was scored as a Super Output Area and includes a range of measures that considers geographical access to a variety of services such as health, education and housing. The IMD 2004 comprises seven domains, with each domain carrying a percentage weighting, as shown in Table 8:4.

**Table 8:4 The English Indices of Deprivation 2004: Summary (revised)**

Domain Weights for the IMD 2004	% Domain Weight
Income Deprivation	22.5
Employment Deprivation	22.5
Health Deprivation & disability	13.5
Education, skills & training Deprivation	13.5
Barriers to housing & services	9.3
Crime	9.3
Living Environment Deprivation	9.3

Source: Office of the Deputy Prime Minister, 2004

The geographical catchment area in this research project lies in the south east of England, which is one of the least deprived areas in the United Kingdom, although much of the area around Basingstoke from which our population is drawn may be described as rural. I have chosen to use the revised IMD 2004 in my research because I believe it is the best tool for providing an overview of rural deprivation. Although rural areas are generally



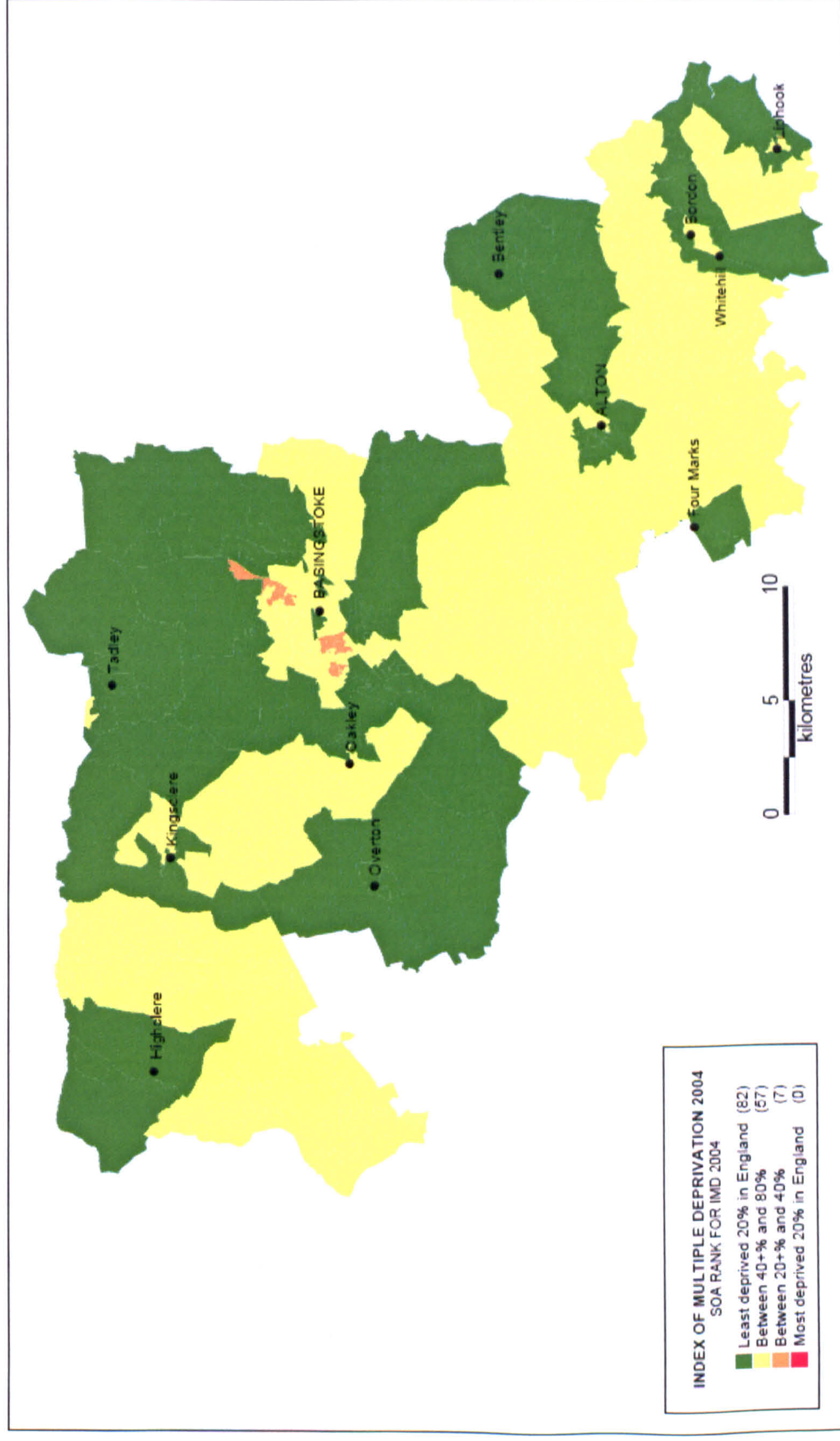
perceived to be idyllic and pleasant places to live, they may also lead to a social isolation, with poor access to local services, due to limited transport services and inadequate housing. All of these factors account for an important type of deprivation, specific to country dwellers. This is shown in Table 8:4 by the weighting of 9.3 for the Living Environment Deprivation domain that matches the weighting apportioned to Crime.

The IMD scores all 998 wards and local authorities in England and in Wales. The area of greatest deprivation is in Liverpool with a score or rating of 86.67. This compares with the area of least deprivation in England, which is in Woking in Surrey, and scores 0.59. Within the Basingstoke area, the least deprived area also scores 0.59 and is to be found in North Waltham and Oakley [Figure 8:4]. The areas of greatest deprivation in the catchment area for my study are in Buckskin scoring 25.99 and Popley East scoring 24.75, both in the Basingstoke town centre [Figure 8:5]. Access and uptake of CR from these areas of greater deprivation is generally less.



### Figure 8:5 Deprivation in the Basingstoke and Alton areas

**The English Indices of Deprivation 2004**  
**Rank of Index of Multiple Deprivation - North Hampshire PCT**

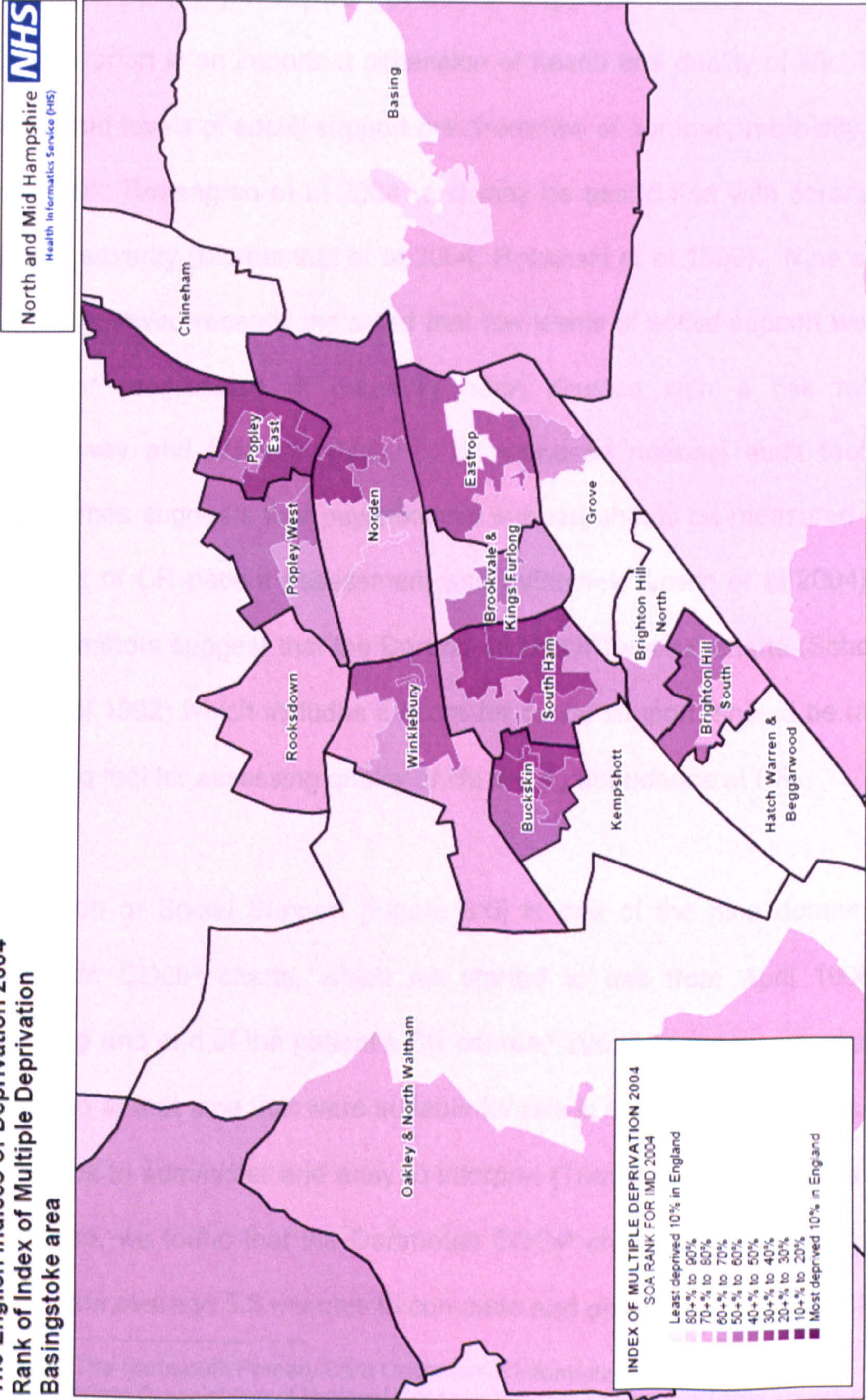


Source: Office of the Deputy Prime Minister, Indices of Deprivation 2004.  
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Figure 8:6 Deprivation in the Basingstoke local area

The English Indices of Deprivation 2004  
Rank of Index of Multiple Deprivation  
Basingstoke area



Source: Indices of Deprivation 2004. The Office of the Deputy Prime Minister.  
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### **8.3.6 Measuring perception of social support**

Social support is an important dimension of health and quality of life. It is well-known that levels of social support are predictive of coronary morbidity (Marmot et al 1991; Rosengren et al 2004) and may be associated with coronary heart disease severity (Blumenthal et al 2004; Rozanski et al 1999). Nine out of ten studies reviewed recently indicated that low levels of social support were a risk factor for progression of coronary heart disease with a risk ratio of 3 (Hemingway and Marmot 1999). The proposed national audit tool for CR programmes suggests that psychosocial support should be measured routinely as a part of CR patient assessment and outcomes (Lewin et al 2004). Lewin and co-authors suggest that the Dartmouth COOP<sup>i</sup>/wonca<sup>ii</sup> charts (Scholten and van Weel 1992) which includes a score for social support, should be used as a screening tool for assessing quality of life during attendance at CR.

Perception of Social Support [Figure 8:6] is one of the nine domains in the Dartmouth COOP charts, which we started to use from April 1996 at the beginning and end of the patient's CR course. We were not aware of any other measures at that time that were suitable for use in CR settings in terms of being both quick to administer and easy to interpret (Turner et al 2003). In a study at our centre, we found that the Dartmouth COOP charts and the HADS took our patients on average 5.5 minutes to complete and only 30 seconds for CR staff to

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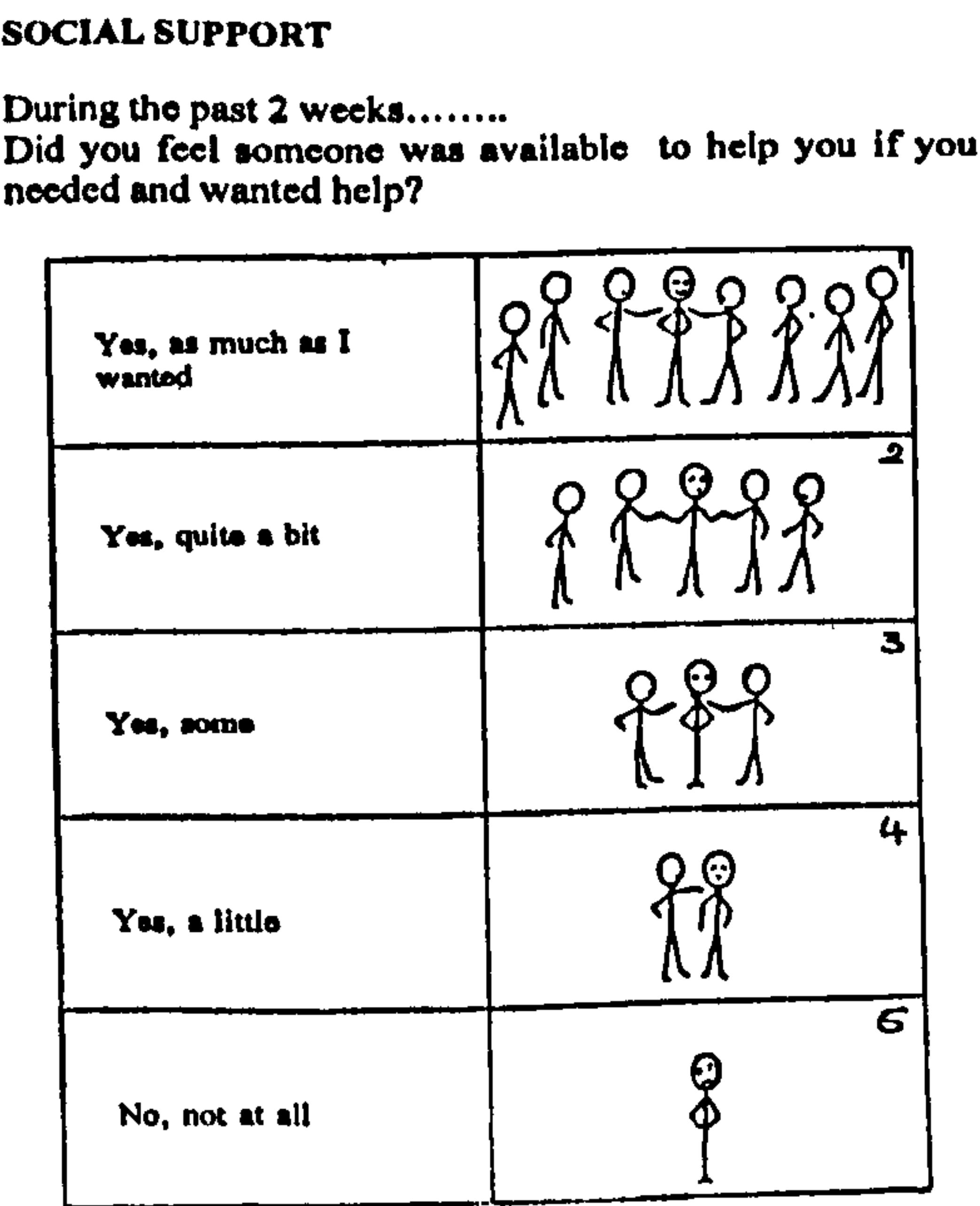
<sup>i</sup> COOP - The Dartmouth Primary Care Cooperative Information Project

<sup>ii</sup> wonca - World Organisation of National Colleges Academies and Academic Associations of General Practices Organisation/Or Family Physicians



score. I have described how we used the charts in Chapter 9. In this study I decided to consider the level of social support recorded at the start of the programme as a baseline demographic measure.

**Figure 8:7 Perception of Social Support (wonca chart)**



**8.4 Determining Outcome**

**8.4.1 Notification of deaths**

The collection of mortality data for this study has involved the use of two different versions of the International Classification of Diseases [ICD]. All death certificates use an international system for recording cause of death. The International Statistical Classification of Diseases and Related Health Problems has been in existence for many years. The original concept of using an internationally agreed code for cause of death was designed to enable mortality

statistics to be compared across different countries in the world as well as facilitating similar methods of collection, processing and presenting mortality statistics. As medical conditions are reported to the authorities, they are subsequently translated into codes governed by rules laid down by the World Health Organisation. In response to developments in medicine over time, the original classification of diseases has been updated several times.

The version in use at the time of writing this thesis is the second edition of the tenth revision, known as ICD-10 (WHO 2000). It was published in 1993, and used in England and Wales from 1<sup>st</sup> April 1995, and in Scotland and Northern Ireland from 1<sup>st</sup> April 1996. Mortality coding, however, using ICD-10 as opposed to ICD-9 was not introduced until January 2001. ICD-10 (Janisch 1990) is considerably different from former versions and far more comprehensive. It is published in three volumes and has twice as many categories as ICD-9 (Glattre 1990). In ICD-10 there have been some radical changes in the grouping of diseases.

Both the ninth and tenth revisions of the ICD use the dagger [†] and asterisk [\*] system to facilitate coding. A dagger sign denotes the primary code for the underlying disease and an asterisk enables an additional code to be added to clarify the cause of death. The asterisk must not be used as the sole code.



8.4.2 Differences between ICD-9 and ICD-10

There are several differences between ICD-9 and the ICD-10. ICD-9 has only 5,000 categories for classifying cause of death and uses a 4 digit numeric structure. The ICD-10 revision contains a further 3,000 categories and a 4 digit alphanumeric design enabling future revisions to occur without disruption to the coding. Many of the chapters in the newer version have been rearranged, which may make comparisons between cause of death difficult for studies such as this one, which straddles both ICD-9 and ICD-10. In ICD-9 nearly all the coronary heart disease codes fall between numbers 410-414 [Table 8:5].

Table 8:5 The differences in descriptions between ICD codes 9 and 10 for the coronary deaths in the cohort

ICD-9 Frequency		Description	ICD-10 Frequency		Description
410	57	Acute myocardial infarction	I219	23	Acute myocardial infarction, unspecified
			I249	1	Acute ischaemic heart disease, unspecified
414.1	1	Aneurysm of the heart			
414	9	Coronary atherosclerosis	I251	13	Atherosclerotic heart disease
414.8	1	Chronic ischaemic heart disease			
414.9	57	Chronic ischaemic heart disease NOS*	1259	56	Chronic ischaemic heart disease, unspecified
			1255	1	Ischaemic cardiomyopathy

\*Not otherwise specified

In ICD-10 coronary heart disease is placed under a heading of 'Circulatory Diseases'. It is more thorough in its application. For example, an acute myocardial infarction is subdivided into six different numerical categories as shown in Table 8:6. According to a recent paper there is a decrease of about 10% in the number of deaths assigned to acute myocardial infarction with the use of ICD-10 in place of ICD-9, although trends in mortality remain unaffected by the change in instrument (Griffiths et al 2004).

**Table 8:6 Subdivisions of the coding for death due to an acute myocardial infarction in ICD-10**

ICD-10: Number	Acute myocardial infarction: Description
I 210	Acute transmural myocardial infarction of anterior wall
I 211	Acute transmural myocardial infarction of inferior wall
I 212	Acute transmural myocardial infarction of other sites
I 213	Acute transmural myocardial infarction of unspecified sites
I 214	Acute subendocardial myocardial infarction
I 219	Acute myocardial infarction, unspecified

However, the death certificates for the patients in this study with a primary cause of death of a myocardial infarction [n=23] coded with ICD-10, as opposed to ICD-9 codes, have all been given the same code, 'I 219'. None of the other myocardial infarction codes has been applied. The causes of death by ICD code for all the patients in the cohort are illustrated in Table 8:7 .



**Table 8:7 Causes of Death ICD-9 and ICD-10**

ICD Code	Frequency	Description
1259	1	Filariasis NOS
1519	4	Malignant neoplasm stomach
1520	1	Malignant neoplasm duodenum
1533	1	Malignant neoplasm sigmoid colon
1536	1	Malignant neoplasm ascending colon
1539	1	Malignant neoplasm colon
1541	1	Malignant neoplasm rectum
1579	2	Malignant neoplasm pancreas
1629	9	Malignant neoplasm bronchus/lungs
1729	1	Malignant melanoma skin
1749	1	Malignant neoplasm breast
1830	1	Malignant neoplasm ovary
185	2	Malignant neoplasm prostate
1889	3	Malignant neoplasm bladder
1912	1	Malignant neoplasm temporal lobe
1990	3	Malignant neoplasm disseminated
2019	1	Hodgkins disease
2041	1	Chronic lymphoid leukaemia
2500	1	Diabetes mellitus uncomplicated
2506	1	Diabetes with neurological manifestations
410	57	Acute myocardial infarction
4140	9	Coronary atherosclerosis
4141	1	Aneurysm of the heart
4148	1	Chronic ischaemic heart disease
4149	57	Chronic ischaemic heart disease NOS
4151	3	Pulmonary embolus/infarct
4241	1	Aortic valve disease
4281	1	Left heart failure
4289	1	Heart failure NOS
430	1	Subarachnoid haemorrhage
4340	1	Cerebral thrombosis
436	6	Cerebrovascular accident
4379	2	Cerebrovascular disease
4411	1	Ruptured thoracic aneurysm
4413	2	Ruptured abdominal aneurysm
4415	1	Ruptured aortic aneurysm
481	2	Pneumococcal pneumonia
485	2	Bronchopneumonia
486	2	Pneumonia
496	2	Chronic airways disease
515	1	Post inflammatory pulmonary fibrosis
585	1	Chronic renal failure
8120	1	Fractured upper end humerus
C509	1	Cancer
C159	4	Cancer
C160	1	Cancer
C169	2	Cancer
C180	1	Cancer

ICD Code	Frequency	Description
C187	1	Cancer
C189	3	Cancer
C20	2	Cancer
C220	1	Cancer
C221	2	Cancer
C259	2	Cancer
C349	18	Cancer
C433	1	Cancer
C439	1	Cancer
C449	1	Cancer
C450	1	Cancer
C459	2	Cancer
C541	1	Cancer
C56	1	Cancer
C61	2	Cancer
C64	2	Cancer
C679	3	Cancer
C719	1	Cancer
C73	1	Cancer
C787	1	Cancer
C80	13	Cancer
C851	1	Cancer
C859	3	Cancer
C911	2	Cancer
C920	1	Cancer
C97	3	Cancer
D430	1	Not cardiovascular
D591	1	Not cardiovascular
E149	1	Not cardiovascular
E780	1	Not cardiovascular
F03	1	Not cardiovascular
G20	1	Not cardiovascular
I119	1	Hypertensive heart disease without congestive heart failure
I219	23	Acute myocardial infarction, unspecified
I249	1	Acute ischaemic heart disease, unspecified
I251	13	Atherosclerotic heart disease
I255	1	Ischaemic cardiomyopathy
I259	56	Chronic ischaemic heart disease, unspecified
I269	1	Pulmonary embolism
I309	1	Acute pericarditis, unspecified
I330	1	Acute & subacute infective endocarditis
I350	1	Aortic (valve) stenosis
I359	2	Aortic valve disorder, unspecified
I472	1	Ventricular tachycardia
I48	1	Acute fibrillation and flutter
I500	2	Congestive heart failure
I510	1	Cardiac septal defect, acquired
I516	1	Cardiovascular disease, unspecified
I609	1	Subarachnoid haemorrhage



ICD Code	Frequency	Description
I619	1	Intracerebral haemorrhage, unspecified
I639	1	Cerebral infarction, unspecified
I64	11	Stroke, not specified as haemorrhage or infarction (CVA NOS)
I679	6	Cerebrovascular disease, unspecified
I713	3	Abdominal aneurysm, ruptured
I739	1	Peripheral vascular disease, unspecified
I802	1	Phlebitis & thrombophlebitis of other deep vessels of lower extremities
J180	8	Not cardiovascular
J182	1	Not cardiovascular
J189	6	Not cardiovascular
J449	2	Not cardiovascular
J841	2	Not cardiovascular
K254	1	Not cardiovascular
K265	1	Not cardiovascular
K529	1	Not cardiovascular
K559	1	Not cardiovascular
K709	2	Not cardiovascular
L024	1	Not cardiovascular
M332	1	Not cardiovascular
N138	1	Not cardiovascular
N179	1	Not cardiovascular
N19	1	Not cardiovascular
NODC	4	No death certificates
R99UC	1	Not cardiovascular
V435	1	Bladder replacement
V494	1	Disfigurement of limbs
X599	3	Not cardiovascular
Y339	1	Not cardiovascular
Total	451	

### 8.4.3 Accuracy of Death Certificates

There are many reasons why information recorded on death certificates may be inaccurate and many researchers internationally have commented on these problems.

The ICD-9 codes were in use when a survey of coronary heart disease deaths in four North American states was performed between 1987 and 1995 (Coady et al 2001). The researchers collected information about the deaths from a variety of sources. They looked at the medical records of the deceased, and conducted interviews with coroners and doctors. They compared the data on the death certificates with the information they had gathered, in particular from the doctors, and identified variations in the accuracy of death certification in the four different regions they had surveyed. They found that coronary heart disease deaths had been overestimated in about 20% of cases and that one in three deaths categorised as coronary heart disease deaths had been incorrectly coded.

A similar review (Chen et al 2002) suggested that the accuracy of death certification worldwide requires improved regulations. The focus of this research was on international methods for recording deaths, and the effect that this might have on the reporting trends in coronary heart disease mortality. Incorrect certification of death was reported to have led to inaccurate use of the ICD codes and, as a consequence, miscoding of cardiovascular outcomes. Moreover, the volume of errors strongly influenced trends in reported mortality from coronary heart disease, a problem that has not yet been resolved (Frasure-Smith and Lesperance 2005).



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Causes of mortality were also misclassified in the WHO-MONICA<sup>iii</sup> Ghent-Charleroi Study (De Henauw et al 1998) according to the researchers who validated the coronary heart disease data that were collected during the Belgium arm of the MONICA trial. Not only were many of the cases miscoded, but the authors also reported a tendency to select to 'other forms of coronary heart disease' rather than to select specific diagnoses.

A further reason for miscoding of death may arise from misdiagnosis. There may be an error in diagnosing the cause of death by the physician in attendance or incomplete reporting of clinical information about the deceased. A paper written for the World Health Organisation (Lozano et al 2001) discusses the problems of misclassification of deaths from coronary heart disease. In several instances a number of ill-defined cardiovascular codes were identified, [Table 8:8] that were being inaccurately assigned to ischaemic coronary deaths. This occurred, for example, when the cause of death was misdiagnosed or the physician certifying the death received insufficient clinical information about the patient. When the Japanese switched from ICD-9 to ICD-10 coding between 1994 and 1995, mortality rates for coronary disease in that one year rose by 25% (Lozano et al 2001).

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<sup>iii</sup> World Health Organisation MONItoring of trends and determinants in CArdiovascular diseases



**Table 8:8 III-defined cardiovascular codes**

Disease	ICD-9	ICD-10
Paroxysmal ventricular tachycardia	427.1	I 472
Ventricular fibrillation & flutter	427.4	I 490
Cardiac arrest	427.5	I 460
Heart failure	428.0	I 500
Myocarditis, unspecified	429.0	I 514
Myocardial degeneration	429.1	I 515
Cardiovascular disease, unspecified	429.2	I 516
Complications of heart disease, unspecified	429.9	I 519
Atherosclerosis, generalised & unspecified	440.9	I 709

Source: (WHO 1992; WHO 1997)

However, the coding of cause of death in the patients in this study is likely to be very reliable since all the people have been under close medical supervision during the timeframe of the study, and known individually by me.

Data from the Office for National Statistics is limited to residents of England and Wales who have registered with a general practitioner. Information on some patients, for instance those who have moved abroad, those without a fixed abode, or those who have failed to register with a general practitioner, will be incomplete. Another problem regarding completeness of information occurs in death certification for people who die abroad. It is unlikely that information about the cause of death will be transferred back to the Office for National Statistics. For example, we know via his spouse/widow, of one patient from our cohort who died in Germany from a myocardial infarction, yet we have no official information from the Office for National Statistics about his death. It may take up to seven years to produce a death certificate in special circumstances, such as in 2005

following the Tsunami. These issues are unlikely to have an important effect on the estimates of mortality in this research.

#### **8.4.4 Coding errors**

Errors in coding are usually due to inaccurate record-keeping by those who have completed the source documentation; for example the physician who certifies the death. The National Health Service Information Authority identifies this as the main reason behind most of the errors found by audits of clinical coding. It is hoped that in future, staff will be trained as coders and be encouraged to complete a national clinical coding qualification in order to provide best practice in this field and limit coding errors.



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# **Chapter 9**

## **Study Methods**

### ***9.1 Study design and ethical approval***

This study is a single centre, ten-year prospective cohort study of patients who have been diagnosed with coronary heart disease. The main outcome in this study is mortality, as recorded by the National Health Service Central Register. Local ethical approval was granted in 2001 from the North and Mid Hampshire Local Research Ethics Committees, for work on this data set. However, since the initial ethics approval was granted, the research proposal has been further developed. Proposed changes to the study were submitted to the local ethics committee once more and approval was received from the ethics committee regarding all the changes that were made to the original research proposal. Throughout the period of study I have adhered to national Data Protection Regulations (Iversen et al 2006).

### ***9.2 Study Aim***

The aim of the study is to establish whether levels of fitness and levels of depression or changes in these levels of cardiac rehabilitation participants are associated with survival time.



### **9.3 Study Hypotheses**

The hypotheses are:

1. The risk of mortality in this coronary population is predicted by:
  - i the initial fitness level as measured by peak exercise performance on an exercise treadmill or a bicycle ergometer
  - ii the level of fitness [as in i] upon completion of Phase III CR
  - iii the degree of change in the level of fitness [as in i] during the Phase III CR programme.
2. The risk of mortality in this coronary population is predicted by:
  - i the severity of depressive symptoms as measured by the Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983) at the time of entry to Phase III CR
  - ii the severity of depressive symptoms [as in 2.i] at the time of discharge from Phase III CR
  - iii the degree of change in depression scores [as in 2.i] during the Phase III CR programme.
3. The risk of mortality in this coronary population is associated with:
  - i a statistically significant interaction between baseline fitness and baseline depression scores at the time of assessment for the Phase III CR programme
  - ii a statistically significant interaction between fitness and depression scores at discharge from Phase III CR

- iii a statistically significant interaction between the change in depressive symptoms and change in fitness level during the Phase III CR programme.

## **9.4 Study Setting**

The study is set in a semi-rural area in Southern England. The Basingstoke and Alton CR programme has been in operation since 1976 and provides both short term and long term exercise programmes and secondary prevention to patients with cardiac illness who live in North Hampshire and adjacent counties. The CR programme is now a part of the Cardiology Department of the Basingstoke and North Hampshire Hospital NHS Foundation Trust in Basingstoke, which was formerly called Basingstoke District Hospital. The CR programme is based in the community in a purpose-built building at Alton, 16 miles south of Basingstoke. The programme also runs at the hospital site and in a community centre at Tadley, 9 miles north of the hospital on the A340.

We receive referrals from cardiologists and general practitioners in neighbouring general hospitals and primary care trusts in addition to the routine referrals from our own network. The catchment area for our programme extends to within a 25-mile radius from our base in Alton [Figure 9:1]. Exercise and health education sessions are offered at three centres: in the hospital physiotherapy gymnasium in Basingstoke, a large hall in a community centre at Tadley and in Alton, where the major part of the service takes place.



There is currently an average of 10 referrals per week. This has increased considerably since 1998, when our first interventional cardiologist was appointed.

The CR Programme offers phases I, III and IV of CR to patients and certain aspects of the CR programme to spouses or partners as well. I described the phases in detail in Chapter 2 page 25. We have never been given sufficient resources to provide Phase II rehabilitation, which includes following up all newly discharged patients in the interval before they commence the exercise programme. The Phase III component lasts between six weeks and six months, according to need, and is offered to all myocardial infarction patients discharged from the hospital and to all patients within our catchment area who are recovering from cardiac surgery or revascularisation.



**Figure 9:1 The main area served by the Basingstoke & Alton Cardiac Rehabilitation programme [from Multimap.com]**



The rehabilitation programme is a standard, comprehensive course, tailored to the individual patient and comprising incremental supervised exercises, home exercises, risk factor monitoring, health education, stress management training and relaxation sessions (Coats et al 1995; West and Jones 1995). The centrepiece is a graduated exercise course lasting six to eight weeks for younger, less severely affected patients and up to six months for older and sicker patients.



All patients are assessed physically and psychologically at the beginning and at the end of the Phase III programme, using standardised and validated measurements. Some patients are offered the Heart Manual (Lewin et al 1992), a home programme of exercise and education, as an alternative to attending the courses, particularly if they do not wish to socialise or if access to one of the venues is difficult. In my study, this applied to only a small group of 24 patients who received the Heart Manual in lieu of attending the CR programme as an out-patient.

The induction and orientation session at the start of the programme, to which partners are invited, helps the patients to be weaned gently into all the aspects of the rehabilitation course. Using medical information about the patient from the hospital discharge summary, the doctor's clinical examination and the exercise test results, the nurses and therapists who supervise this session help to formulate an individualised plan for each patient. The format of the course is explained to them and they are taught the importance of reporting changes in symptoms or anything else that could affect their treatment or progression through the course.

#### **9.4.1 Staffing**

A multidisciplinary team of health care professionals is involved in rehabilitating the cardiac patients referred to the programme. Two physicians

staff on a regular basis. The main referral route is via the Royal Brompton Hospital, London but we receive patients from other centres namely St George's Hospital and University College Hospital, London and the Southampton Group of Hospitals. Private patients are referred into the programme from a variety of venues. Ideally surgical patients are referred immediately after their discharge from hospital and are given an appointment to start their rehabilitation at about six weeks after the date of their operation.

#### **9.4.3 The Exercise Programme**

The type of exercise performed within the supervised exercise class and at home is aerobic. Circuit training is the most convenient and effective style of exercise for cardiac patients. Circuit training requires the patient to perform various exercises at different stations using a mixture of upper and lower limb muscles. These can alternate between pure aerobic exercise and muscle, strength and endurance exercises, which act as active recovery exercises, allowing the patient to exercise for about 40 minutes in total. The duration of each session depends upon the individual's current physical ability. Supervised circuit training sessions are performed once or twice weekly, the sicker patients being encouraged to attend more often than those with less severe disease. Homework is set for the remaining days of the week and includes home circuits and brisk walks, where feasible, so that exercises are performed on most if not every day each week.



#### **9.4.4 The Health Education and Stress Management programmes**

Other components of the programme include education, stress management, relaxation training and risk factor monitoring. The health education programme consists of a series of lectures that cover various topics such as understanding coronary heart disease, cholesterol, healthy eating, blood pressure, the benefits of regular physical activity, smoking, cardiac medications, and stress management and relaxation techniques. The patients' partners are invited to join in this part of the rehabilitation programme. At the start of CR all the patients complete two questionnaires to assess their psychosocial condition. This helps to identify those patients who present with anxiety or depression and who may require extra support whilst they are in the programme, together with encouragement to attend the stress management and relaxation sessions. All the patients are given their own handheld records, which contain information to backup that given in the lectures, as well as their own personalised exercise homework diary pages for recording their activities on the five days when they performed their exercise routine without medical supervision.

#### **9.5 *Data collection and management***

At the start of the Phase III CR, patients referred to the programme have an initial clinical examination, which includes formal exercise testing by either treadmill, or bicycle ergometry, with ECG monitoring and measurement of estimated peak workload.

We also take a full clinical history from the patient and record other baseline biological and clinical measurements during the patient's first visit to the Phase III programme. This includes taking the pulse to measure a resting heart rate, and also measuring the patient's blood pressure. In particular we note any relevant co-morbidity that may affect the patient's exercise prescription. For example co-morbidity often accompanying diabetes, such as peripheral neuropathy or silent ischaemia, may affect the type of exercise programme designed for patients with diabetes.

At this first visit we ask the patients to bring us a list of their current medications so that this information can be documented. We also request them to have a fasting blood test performed within the following 6-week period to measure lipid sub-fractions. The local pathology department is asked to send a copy of the test results to the CR Unit to be recorded onto our patient database.

The information we gather is recorded in each patient's notes and on the database and passed on to the rehabilitation team that looks after the patient during Phase III. The various components of rehabilitation are tailored to meet the individual's requirements. All clinical measurements are repeated when the patients finish their programme, and results of blood tests discussed with the patient either during the programme or at their final visit.

Since 1993 the CR Programme has compiled a computerised database of patient characteristics and outcomes in a Microsoft Access database file



(Microsoft 2000). Initially all information about the patients was recorded in paper format. We have retrospectively transferred information from the original paper records for each patient into the electronic format in the form of a template to facilitate audit and research. An example of the template used to record this information is shown in Figure 9:2.

Figure 9:2 The Access Database Template

ALL PATIENT DETAILS

PatientID: 5613

Last Name:

First Name:

Known as:

Sex: m

Tadley: ☐

NHH: ☐

Address1:

Age:

Birthdate:

Ethnicity: a

Year: 2005

Village:

GP:

Hospital: NHH

Rehab start:

Town: Basingstoke

Hosp Cons: Dr Bishop/Dr Brookes

Source:

Date illness:

County: Hants

Graduate Date:

PP: ☐

HM: ☐

OP: ☐

Occ Code:

Post Code:

Phone:

Mobile:

Employment:

Ref.Diagnosis:

Marital statue:

Other cardiac:

Diabetes: ☐

Co-morbidity:

Thyroid: ☐

Height:

Clgs-hist:

Clgs-b:

Clgs-af:

Family History: ☐

BEFORE AFTER

Cholesterol:

HDL:

LDL:

Entry code:

Weight:

Triglycerides:

VO2-before:

after:

Troponin:

BMI:

Sugar:

after:

Past ex habit:

Waist : 0 0

TSH:

RISK CATEGORY:

BEFORE AFTER Score:

BP:

T4:

after:

Anxiety:

MEDICATION: BEFORE AFTER

Overall hith: BEFORE AFTER

Feelings: BEFORE AFTER

Depression:

Aspirin: Yes

Life in gen: BEFORE AFTER

Painful ten: BEFORE AFTER

Analogue:

ACE inhil: Yes

Long-term exercise:

Physical fit: BEFORE AFTER

Social sup:

B-blocker figures:

Additional Infomation:

Exit code:

Statin: Yes

ETT: Bruce Protocol

Anti-arrhythmic:

mins secs to heart rate of Borg Scale

Thyroxine:

Before After

Amlodarone:

After

Diltiazem:

Hypoglycaemic :

Current THR:

RHR:

NSF

Rehab Phase III sessions:

Rehab Phase IV: ☐

Home Programme: ☐

Smoking: ☐

Phase IV elsewhere: ☐

Not known: ☐

BMI:

NFRI: ☐

NFRI date:

Risk factor score: 0

Weekly ex sessions:

Cardiac RIP: ☐

date RIP:

Sudden death: ☐

MI: ☐

Heart failure: ☐

Not stated: ☐

1 year comment:

CofDeath:

ICD code:

Duplicates:

BNP:



For each patient we have collected a range of measures that reflects both physical and psychosocial status at the start of and upon completion of Phase III CR [Table 9:1].

**Table 9:1 Baseline demographic and outcome measures collected by the cardiac rehabilitation programme staff on all the patients enrolled into the programme**

1	Name, gender, marital status, age, height and weight
2	Reason for referral for cardiac rehabilitation
3	Former exercise habit
4	Employment status – occupational coding (Standard Occupational Classification, 2000)
5	Medication at the start and end of the Phase III exercise programme
6	Response to electrocardiograph stress test: time on treadmill or bicycle ergometer, heart rate, perception of effort rating (Borg 1982)
7	Before and after measures of physical fitness via an estimated VO <sub>2</sub> from treadmill or bicycle testing, (Astrand and Rhyning 1954)
8	Anxiety and depression scores using the Hospital Anxiety and Depression scale (Zigmond and Snaith 1983)
9	Quality of life scores using the Dartmouth Coop charts /wonca (van Weel 1993)
10	Number of supervised exercise sessions attended whilst participating in CR
11	Adverse events which occurred during CR
12	Diabetes
13	Smoking habit
14	Body mass index
15	Blood pressure readings
16	Blood cholesterol and triglyceride levels
17	Thyroid function test results
18	Future intentions for long-term exercise habit or arrangements to attend a Phase IV cardiac rehabilitation programme
19	Co-morbidity – details of cardiac and non-cardiac illness, such as diabetes, concurrent medical conditions other than index cardiac event that may or may not limit ability to participate in CR (Zoghbi et al 2004)
20	Postal code to be related to an Index of Deprivation (ODPM 2004)



### **9.5.1 Data collection on the fitness levels of the coronary patients**

Measures of fitness are estimated from the exercise tests that the patients perform at their initial assessment at the start and on completion of the Phase III programme as described in Chapter 8.

Exercise testing provides the following information:

- initial fitness level – this helps to decide the level of exercise that can be prescribed. It also provides a baseline with which to compare fitness at the end of the programme – a measure of the effectiveness of the course.
- heart rate response to exercise – from which exercise heart rate targets can be set.
- ECG changes during exercise – including reversible ischaemia and exercise induced arrhythmias. The presence of either affects exercise prescription.
- future risk – exercise test responses such as fitness level, blood pressure response and arrhythmias contribute to risk assessment.

The purpose and value of the risk stratification process in CR is discussed in Chapter 8 on page 193.

### **9.5.2 Exercise testing of the coronary patients during the study period**

The exercise tests were overseen by one of the two doctors involved with the CR programme. They were performed on either a bicycle ergometer or an

exercise treadmill. Either system incorporated a facility for monitoring and recording a continuous ECG on each patient during the exercise tests.

The bicycle ergometer used was a Cardionics mechanically-braked bicycle. The loads used on the bicycles ranged from 0.25 kilograms and up to 3.00 kilograms. This equated to workloads of between 12.5 watts and 150 watts. The choice of load depended upon the doctor's perception of the patient's physical capability at the start of the test, which included accounting for their age, the size of the infarction if relevant, and whether or not they had a history of angina. The patient pedalled at a constant 50 revolutions per minute. A metronome was used to keep the speed of pedalling constant throughout the test. The workload on the bicycle ergometer was increased in a staged fashion every 5 minutes. The blood pressure was measured to the nearest 5mmHg before the test and during the last 30 seconds of each 5 minute stage of the protocol. The  $VO_{2peak}$  was predicted from the ergometer test from the known energy cost of cycling at the different loads, measured in watts and converted to ml/kg/min by dividing predicted oxygen uptake by the patient's weight.

The treadmill used was part of the Marquette Mach 15/17 Electro-cardiographic system. Patients were not allowed to support themselves on the treadmill bar whilst they performed the test. The exercise test protocol for the treadmill tests was either the full Bruce or the modified Bruce protocol. (Bruce 1973). These tests are the two most commonly used in the United



Kingdom. The modified Bruce was used for frailer patients, as it starts at two stages below that of the Bruce and is gentler to perform.

The Bruce protocol starts with the patient walking at a gradient of 10% at 1.7 miles per hour (mph). Each stage lasts 3 minutes and rises incrementally to a maximum gradient of 22%, a maximum speed of 6mph and a maximum duration of 21 minutes. The modified Bruce protocol starts on the flat at 0% gradient and a speed of 1.7mph at 2 stages below the full Bruce protocol. The stage 3 of the modified Bruce protocol equates with stage 1 of the full Bruce protocol [Table 8:1].

To measure the change in physical fitness during the CR programme the final exercise test was performed at completion of CR, to the same heart rate as the initial test. The oxygen uptake  $VO_{2peak}$  was predicted on the treadmill test on the assumption that each minute of the Bruce protocol uses one metabolic equivalent known as a 'MET' (3.5ml/kg/min) and the first two stages of the modified Bruce protocol use one MET each. For instance, if a patient completes 6 minutes of the Bruce protocol an estimated  $VO_{2peak}$  for the patient is calculated as follows:

The total exercise time completed on the protocol in minutes is multiplied by 3.5 and then a further 3.5 is added to this figure to represent the resting

metabolic rate in millilitres of oxygen for each patient, as shown in the following equation:

$$\text{estimated VO}_2 = 3.5 ( 1 + x )$$

[where x equals time on treadmill in minutes]

A patient completing exactly 2 stages or 6 minutes of the Bruce protocol will have an estimated  $\text{VO}_{2\text{peak}}$  of 24.5ml/kg/min.

$$\text{estimated VO}_2 = 3.5 ( 1 + 6 ) = 24.5$$

[where x equals time on treadmill in minutes]

The tests were terminated when the doctor supervising them noted that either the patient had reached 85% of their predicted heart rate maximum for their age, or if they developed symptoms, which precluded the test's continuation.

The presence of any of the following signs was also a clinical reason for curtailing the exercise tests:

1. angina pectoris or signs of malignant ischaemia on the electrocardiograph
2. multifocal ventricular ectopic beats on the electrocardiograph or other dangerous or compromising cardiac arrhythmias
3. exhaustion or excessive dyspnoea
4. orthopaedic limitations.

Fitness testing is also discussed in Chapter 8, page 186.



### **9.5.3 Data collection on the psychological state of the coronary patients**

Questionnaires were used to ascertain the psychological status of all the CR patients in the study. From 1st January 1993 all new patients enrolled into the programme have been asked to complete the HADS questionnaire as a screening tool (Zigmond and Snaith 1983) [Chapter 8 Figure 8:3] before starting the exercise programme and as an outcome measure when they graduate from the exercise component of the Phase III programme.

From April 1996 all patients were also asked to complete six of the nine Functional Health Assessment charts known as the Dartmouth Coop/wonca Charts (Nelson et al 1987; Scholten and van Weel 1992; van Weel 1993). The combination of the HADS and wonca charts was chosen to explore both psychological health (the anxiety and depression scores) and perceived quality of life (the Dartmouth Coop/wonca charts) during the period of CR.

The charts are a collection of pictorial questionnaires that focus on domains of quality of life. For this study we used six of the domains to assess “overall health”, “life in general”, “feelings”, “painful tension”, “physical fitness” and “social support”. Each domain represented by a pictogram is scored between 1 and 5 where 1 is equal to a rating of excellent and 5 equals a rating of poor. The social support domain was particularly relevant in this research because low levels of social support have been shown to be associated with depression (Barefoot et al 2003; Grant et al 1988). A copy of

the wonca social support chart can be seen in Chapter 8, page 208 [Figure 8.7].

Both the HADS and the Dartmouth charts questionnaire have since been incorporated as CR outcome measures in a national CR audit project as part of a minimum data set for CR launched early in 2006 (Lewin et al 2004).

The CR team members supervised the administration of the questionnaires in order to ensure consistency. They were also familiar with the scoring systems and were able to detect any misinterpretations by the patients as they completed them. At the end of the course all finishers were asked to complete the same questionnaires once more.

Methodological issues regarding the use of questionnaires for coronary patients are discussed in Chapter 8, page 188.

#### **9.5.4 Study participants included in the study**

Although we treated a range of cardiac conditions during the study period, this research focuses only on the patients with coronary heart disease who were enrolled into the CR programme.



**Table 9:2 Primary diagnosis and reason for referral to cardiac rehabilitation during the study period**

Code	Primary Diagnosis
1	Myocardial Infarction
8	Myocardial Infarction with Percutaneous Transluminal Coronary Angioplasty as a single episode of care
3	Percutaneous Transluminal Coronary Angioplasty with or without stenting
2	Coronary Artery Bypass Grafting
4	Angina Pectoris
5	Valve Surgery
6	Other cardiac conditions – such as cardiomyopathy, ischaemic and non-ischaemic heart failure
7	Non-cardiac conditions

At their initial assessment we logged all the patients with an entry code [Table 9.2] and I removed the cardiac patients who did not have coronary disease, for example those who had cardiomyopathy or mitral valve disease from the study database, as described later on in this chapter. I selected the patients with ischaemic heart failure from entry code 6 to include in the study data set.

All of the patients therefore in this study had a diagnosis of either unstable or stable coronary disease as defined by codes from the ninth and tenth revisions of the International Classification of Diseases (ICD-9 and ICD-10). Briefly this relates to codes 410 – 414 in ICD-9 and all the codes prefixed with an 'I' standing for ischaemic in ICD-10. This is better illustrated in Chapter 8 [Table 8.5]. Patients in these categories who joined the study were followed up for up to 13 years following their initial enrolment.

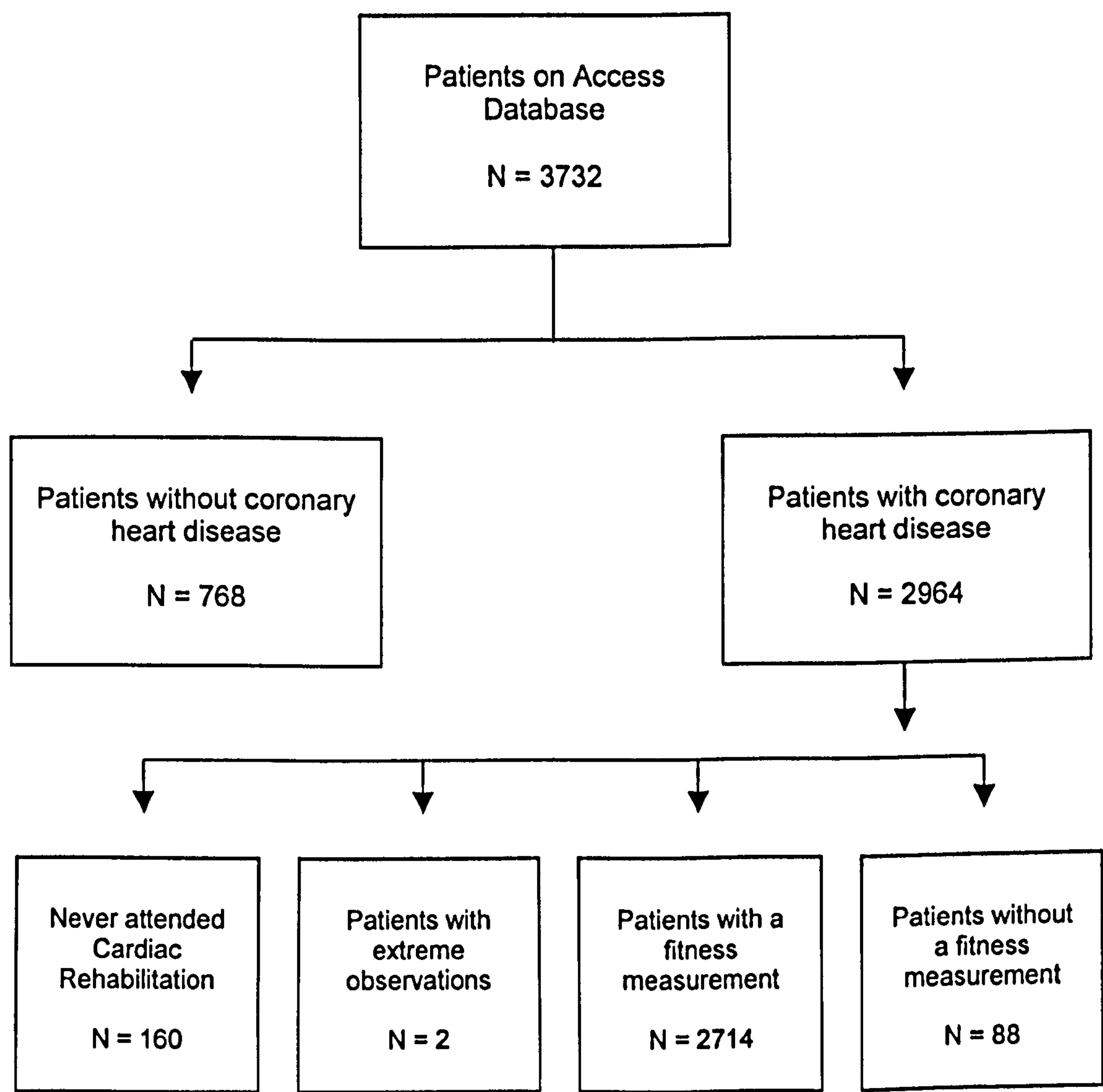
There were 3,732 patients recorded onto our database over the 10-year period of the study [Figure 9.3]. These records included patients who had more than one episode of care during the study, patients who never turned up for their first assessment, and those who were either inappropriately referred or misdiagnosed. Following the removal of 768 patients who did not have a diagnosis of coronary heart disease, there remained 2,964 coronary heart disease patients on the database, of whom 160 did not take up the initial invitation to attend CR. In addition, I found three patients whom I considered to be outliers because of their extreme presentations. One of these was an anorexic with a body mass index of 12. Her myocardial infarction may have been secondary to anorexia nervosa. The second patient was 18 years old and was possibly a miscode or had an obscure genetic condition. These first two observations were excluded from the data at this point. The third outlier was a patient with a cholesterol level of 1.9, who was taking 80mg. of simvastatin<sup>1</sup> at the start of CR. Although this dose of simvastatin is not unusual now, none of the others in the cohort were on a dose of simvastatin greater than 40mg. The majority were taking 10 or 20mg. tablets once a day. I therefore coded this patient's cholesterol as 'missing', and he remained in the data set.

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<sup>1</sup> simvastatin – a cholesterol lowering medication



**Figure 9:3 Patients recorded onto the Access Database between 01.01.1993 and 31.12.2002**



There were 2,714 patients who were assessed with a fitness test at the start of the programme and 88 who joined the programme for whom we have no measure of fitness because they were unable to perform a fitness test. Of the 2,714 patients who underwent fitness testing, 2,054 (75.7%) completed the CR Phase III programme and 660 (24.3%) patients failed to complete the programme. When we knew the reasons for this they were entered in the database. Some patients for example were waiting for revascularisation or

developed significant co-morbidity that subsequently prevented them from continuing to exercise in the Phase III programme.

Other reasons for leaving the programme included being diagnosed with cancer or having an exacerbation of a cancer. Other patients moved away from the area and were referred when feasible, to appropriate rehabilitation programmes, some died in the period between invitation and attendance, a few had difficulty in accessing any of our community venues providing a CR service, and some chose not to perform a home-based programme.

#### **9.5.5 Follow up of the study participants and flagging the data set**

To obtain data on the causes of death we worked with the medical research department of the Office for National Statistics, which is based at the General Register Office in Southport. We supplied them with a list of the patients in the study in an Excel CSV<sup>ii</sup> file. Using an automatic flagging process, and if necessary operator tracing and flagging, I was notified every 3 months of those patients who had died and sent a copy of their death certificates. This allowed me to update the database record at regular intervals.

This study straddles two versions of The International Statistical Classification of Diseases - the 9<sup>th</sup> and 10<sup>th</sup> Revisions. The problems and limitations of applying diagnostic codes and the accuracy of the Office for

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<sup>ii</sup> CSV = comma separated value



National Statistics information are discussed in greater detail in Chapter 8, page 210.

#### **9.5.6 Preparation of the data set and data cleaning**

The following section explains how the raw data from the Access database was prepared for analysis.

Each patient record contained over 100 fields for inputting data. My first task was to decide which fields should be exported into an Excel database for sorting and initial data checking. At this stage the data was anonymised and 50 fields were selected for export, although I retained a copy of the Access database from which I derived the export query. This was necessary as inevitably records required cross checking, even after export. In order to check for outliers and operator errors in data handling, each field was sorted alphabetically in Excel, as it is not possible to do this within Access. The 50 fields of raw data were then prepared for export into Intercooled STATA Version 9 (STATA 2003) for final cleaning and analysis. STATA only accepts Excel files in a CSV format so I adapted some of the fields in order for them to be accepted into the STATA programme.

I made the following adjustments to the data set:

Blood pressure measurements had been entered into Access as a single field. I used an Excel formula to split blood pressure figures into separate cells representing systolic and diastolic readings.

I scored co-morbidity using the Modified D'Hoore Index (Zoghbi et al 2004) and then added the co-morbidity fields.

I used an Access query to send the file of postcodes to a public health information analyst at The North and Mid Hampshire Health Informatics Service who was able to match the pre-calculated Index of Multiple Deprivation [IMD] (ODPM 2004) score to each postal code for me. All but 121 postal codes were matched in this way and returned in Excel format. Postcode linking was complicated by the fact that the Royal Mail had made changes to postcodes in our area over the past ten years. There were major changes to some of the Basingstoke codes in 1995 and some changes to the Alton area codes in December 2000. Two patients had postcodes in Wales, and were not covered by the IMD.



I created a new variable called 'Secondary Prevention' to log whether the patients were taking secondary prevention medication or not, ie aspirin, a  $\beta$  blocker<sup>iii</sup>, ace inhibitor<sup>iv</sup> and a statin.

I coded smoking habit into the following 5 categories: non-smoker, not smoked for more than 10 years, not smoked for between 1-10 years, recent quitter of less than one year and current smoker.

I exported the data from the Excel database into STATA for final preparation and carrying out the analyses. Mortality data, previously entered into Access, continued to be added to the STATA data set up to 15<sup>th</sup> November 2005. The data was rechecked again for outliers and errors and corrected in my initial STATA analysis until the data set was accurate.

## **9.6 Data analysis**

The statistical analyses were performed using the intercooled STATA version 9 package. Survival time was defined as the date the participant joined the Phase III CR programme, which was usually the day of the first exercise test, until the date of death, or 15<sup>th</sup> November 2005.

Fitness was treated as a categorical variable. I used the same three cut off points of  $VO_{2peak}$  as Kavanagh had described in his study of survival in male

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<sup>iii</sup>  $\beta$  blocker - a drug that slows the heart rate, reduces blood pressure and protects the heart after a myocardial infarction

<sup>iv</sup> Ace inhibitor – a drug that reduces blood pressure and is also cardio-protective

CR participants (Kavanagh et al 2002). These were low fitness which equated to a  $VO_{2peak} < 15$  ml/kg/min, medium fitness  $VO_{2peak} \geq 15$  up to 22 ml/kg/min, and high fitness, which was the referent, as a  $VO_{2peak} > 22$  ml/kg/min. Depression was categorised in a similar way. The referent was no depression, which represented a score  $< 8$  on the HADS, symptoms suggestive of borderline depression  $\geq 8$  and  $< 10$ , and symptoms suggestive of clinical depression for scores  $\geq 10$ .

For the descriptive analyses the continuous variables were tested to see if they were normally distributed by creating histograms. When this was the case, the means and standard deviations were calculated for the normally distributed variables and T tests were used to compare differences in continuous variables by groups of participants. ANOVA tests were used when comparing more than two groups. I calculated the median, 10<sup>th</sup> and 90<sup>th</sup> percentiles with variables that did not appear to be normally distributed and used non-parametric tests to test for significance.

Survival analyses were carried out with  $VO_{2peak}$  at baseline as the predictor variable of interest in relation to both all-cause and cardiovascular mortality. The Cox proportional hazards model was fitted and risk factors identified from some of the variables as potential confounders of the relationship, were entered into the basic model. The method I used to perform this part of the analysis and to obtain my fully adjusted model is described in detail in Chapter 11.



Similar analyses were conducted for  $\text{VO}_{2\text{peak}}$  measures at the end of CR and for the change measure from baseline to discharge. I repeated the same process for the three measures of depression. The interaction of fitness and depression was also assessed in the Cox proportional hazards model. This interaction term was adjusted for the known risk factors of the disease as above. Three survival analyses were performed using the interaction at baseline, at discharge and the change from baseline to discharge.

## Chapter 9: References

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# Chapter 10

## Results from Descriptive Analyses

### *10.1 Introduction*

Data from 2,962 participants were available for analyses of whom 248 did not have any fitness data.

Those participants without fitness data will not be included in the main analysis. Table 10:1 compares those participants with and those without fitness data. The participants without fitness data were older, more likely to be female, had greater co-morbidity and were less likely to have received any form of revascularisation procedure.

A flowchart [Figure 10.1] shows the study participants with and without fitness data during the various stages of the CR programme. For all subsequent analyses I used a cohort of the 2,714 study participants, all of whom had a recorded level of baseline fitness at the start of CR, because one of my hypotheses is based on the prognostic effect of levels of physical fitness.

Table 10:1 Demographic and clinical data by whether a measure of fitness data is available (n = 2962)

	Participants with fitness data		Participants without fitness data		p value
	N	Mean (sd)	N	Mean (sd)	
Age, years	2714	61.8 (9.94)	*242	69.1 (11.3)	<0.001 <sup>a</sup>
Gender, female	547	Percentage 20.20	90	Percentage 36.30	<0.001 <sup>b</sup>
Completed rehabilitation	2054	75.70	34	13.70	<0.001 <sup>b</sup>
Diagnostic category					0.001 <sup>b</sup>
Myocardial Infarction (MI)	1451	53.50	155	62.50	
Coronary Artery Bypass Grafts	689	25.40	46	18.60	
PCI (Angioplasty)	251	9.25	34	13.70	
Angina Pectoris	169	6.23	7	2.82	
Other coronary heart disease pathology	54	1.99	3	1.21	
MI+ PCI	100	3.68	3	1.21	
Co-morbidity					
No co-morbidity	1909	70.30	45	51.10	<0.001 <sup>c</sup>
Some co-morbidity	805	29.70	43	48.90	
Family history of coronary heart disease	1212	44.70	27	10.90	<0.001 <sup>b</sup>
Index of Multiple Deprivation score	2600	Median (10th & 90th percentiles) 6.71 (2.86,18.4)	241	Median (10th & 90th percentiles) 7.98 (2.86,18.6)	0.028 <sup>d</sup>

\*Ages were not recorded for 6 participants

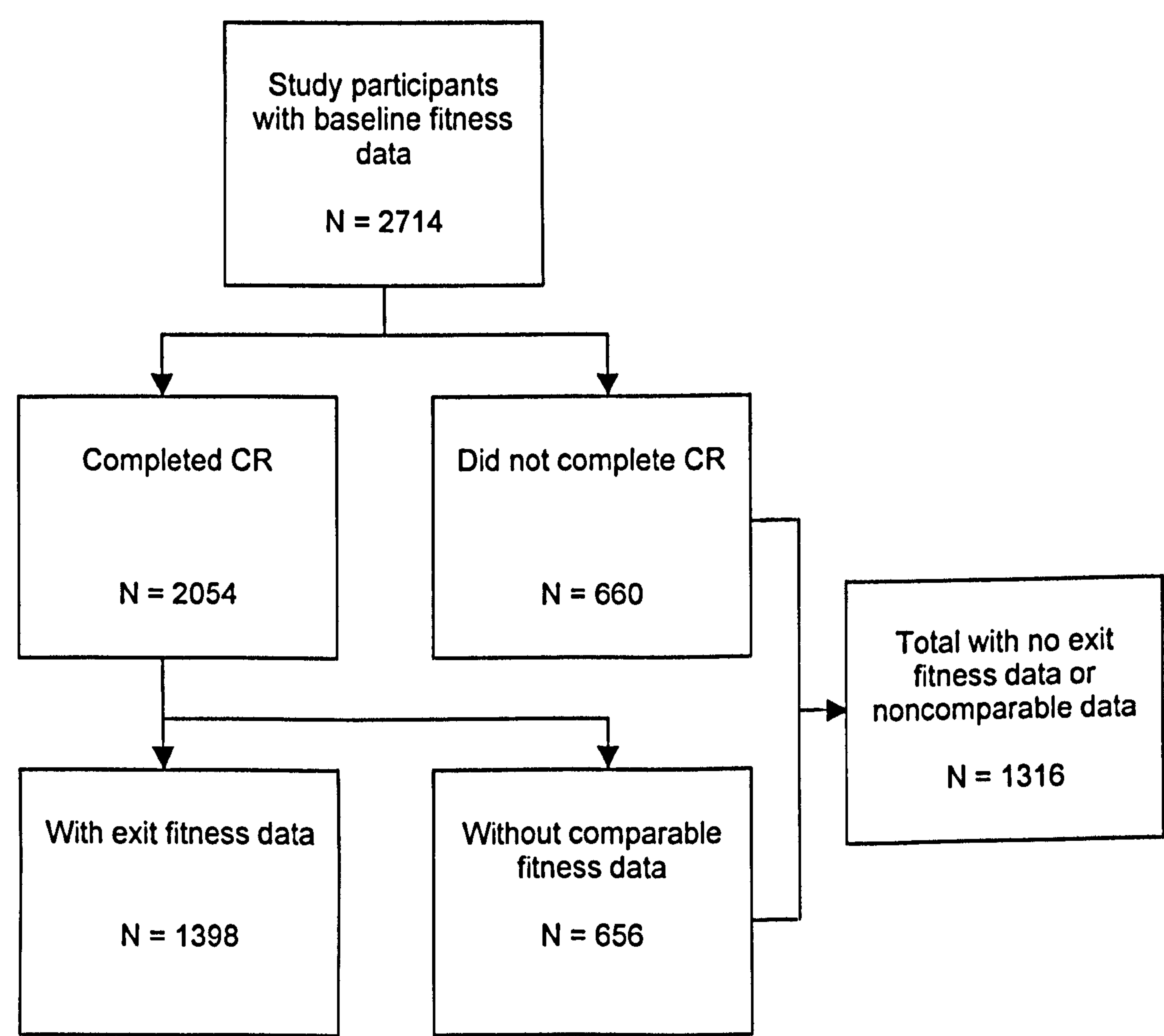
a T test

c Fisher's exact test

d Mann Whitney U test



**Figure 10:1 Flowchart of study participants with and without exit fitness data**



**10.2 Completeness of data for the study participants**

**10.2.1 Missing data**

There were several reasons why data were missing from some of the variables. For example, body mass index data, requiring values for height and weight, were not routinely recorded until 1998 and were only available for 57.2% of participants. Previously participants were weighed but their heights were not recorded. Some blood cholesterol test results were missing, although every participant was given a blood test form at their first assessment and asked to arrange the test.

### 10.2.2 Outcome data

There were 2,054 participants who completed the CR programme and 660 who failed to complete the programme [Figure 10:1]. Table 10:2 shows a comparison between participants who completed CR and those who did not. There were significant differences ( $p<0.001$ ) between several variables. For example there were twice as many current smokers in the group who did not complete CR. A greater proportion of participants from elementary occupations did not complete, and conversely a higher proportion of manager and senior officials completed the CR programme ( $p<0.006$ ). There was also a significant difference between the two groups in their perception of the amount of social support they were receiving at the time of their first assessment. For those who reported that they had no social support at all, there was over three times the percentage [4.48%] found in the group that did not complete compared with those in the group who did [1.47%] ( $p<0.001$ ). There were differences in baseline fitness levels and psychological measures between those who completed and those who did not complete CR. Those who did not complete were less fit ( $p<0.001$ ), more anxious, ( $p<0.001$ ) and more depressed ( $p<0.001$ ), than those who had completed CR.



Table 10:2 Demographic, clinical and lifestyle data by whether participants completed the cardiac rehabilitation programme

	Completers		Non-completers		p value
	N	Mean (sd)	N	Mean (sd)	
Age, years	2054	61.8 (9.73)	660	61.6 (10.5)	0.586 <sup>a</sup>
Systolic blood pressure, mmHg	2047	139 (25.5)	652	139 (27.1)	0.566 <sup>a</sup>
Diastolic blood pressure, mmHg	2042	79.5 (12.8)	646	79.1 (12.9)	0.491 <sup>a</sup>
Gender		Percentage		Percentage	0.01 <sup>b</sup>
Male	1663	81.0	504	76.4	<0.001 <sup>b</sup>
Female	391	19.0	156	23.6	
Diagnostic category					
Myocardial Infarction (MI)	1044	50.80	407	61.70	
Coronary Artery Bypass Grafts	573	27.90	116	17.60	
PCI (Angioplasty)	197	9.59	54	8.18	
Angina Pectoris	115	5.60	54	8.18	0.041 <sup>b</sup>
Other coronary heart disease pathology	40	1.95	14	2.12	
MI+ PCI	85	4.14	15	2.27	
Reported family history of CHD	940	45.80	272	41.20	

<sup>a</sup>T test

<sup>b</sup>Chi square test

	Completers		Non-completers		p value
		Percentage		Percentage	
<b>Smoking habit</b>					<0.001 <sup>b</sup>
Non-smoker	636	31.00	177	26.90	
Not for > 10 years	596	29.00	143	21.70	
Not for between 1-10 years	78	3.80	28	4.26	
Recent quitter < 1 year	603	29.40	215	32.70	
Current smoker	140	6.82	95	14.40	
<b>Reported previous history of diabetes</b>	240	11.70	101	15.30	0.015 <sup>b</sup>
<b>On full secondary prevention medication</b>	384	18.70	144	21.80	0.078 <sup>b</sup>
<b>Co-morbidity score</b>					0.003 <sup>b</sup>
None	1491	72.60	418	63.30	
1 (least)	233	11.30	86	13.03	
2	278	13.50	119	18.03	
3	33	1.61	24	3.64	
4 (most)	19	0.93	13	1.97	
<b>Occupational Code 1-9</b>					0.006 <sup>b</sup>
Managers & senior officials	321	17.30	81	14.50	
Professional occupations	189	10.20	66	11.80	
Associate professional	207	11.10	44	7.86	
Administrative & secretarial	229	12.30	53	9.46	
Skilled trade	447	24.00	135	24.10	
Personal service	60	3.22	16	2.86	
Sales & customer	49	2.63	21	3.75	
Process, plant & machines	211	11.30	82	14.60	
Elementary occupations	148	7.95	62	11.10	



		Completers		Non-completers		p value
<sup>b</sup> Chi square test						
		Percentage		Percentage		
Perception of level of social support						<0.001 <sup>b</sup>
Yes , as much as I wanted		987	66.10	253	56.70	
Yes, quite a bit		279	18.70	99	22.2	
Yes, some		134	8.98	37	8.30	
Yes, a little		71	4.76	37	8.30	
No, not at all		22	1.47	20	4.48	
		Median (10 <sup>th</sup> , 90 <sup>th</sup> percentiles)		Median (10 <sup>th</sup> , 90 <sup>th</sup> percentiles)		
Weight, kg		2045	79.0 (63.0, 98.0)	649	79.0 (61.0, 101.0)	0.983 <sup>d</sup>
Body mass index, kg.m <sup>2</sup>		1176	26.7 (22.7, 32.7)	376	27.4 (22.7, 34.7)	0.045 <sup>d</sup>
Estimated VO <sub>2</sub> ml/kg/min		2054	19.5 (10.5, 29.6)	660	16.3 (8.7, 26.5)	<0.001 <sup>d</sup>
Depression score		2008	3 (1,8)	617	4 (1,10)	<0.001 <sup>d</sup>
Anxiety score		2008	6 (1, 11)	617	7 (2, 13)	<0.001 <sup>d</sup>
Cholesterol, mmol/L		1835	4.9 (3.6, 6.6)	342	5 (3.7, 7.0)	0.047 <sup>d</sup>
Fasting triglycerides, mmol/L		1618	1.43 (0.79, 2.85)	309	1.5 (0.85, 3.31)	0.024 <sup>d</sup>
Index of Multiple Deprivation score		1964	6.26 (2.44, 17.2)	636	8.11 (3.09, 18.7)	<0.001 <sup>d</sup>

Outcome fitness data recorded at the end of CR and change in fitness from start to finish of CR was available for 1,398 [68%] of completers and change in depression score data in 1,939 [94.4%] completers. For all the changes in values from baseline to outcome there were missing data. There were many reasons why outcome data were not available or complete. For example, sometimes there was only a baseline value recorded and not an outcome value, and conversely on occasions an outcome value had been documented but no baseline value.

I was able to calculate changes in fitness levels for 68.1% of study participants. There were several reasons to account for the missing fitness data for 31.9% of the cohort. In some cases the results from the first exercise test at the start of CR were not comparable with the second test performed at the end of the exercise programme. This was because of changes in medication, such as  $\beta$  blocker dosage, between the two tests, which altered resting and working heart rate responses. Four low risk and fitter participants were referred straight into a Phase IV exercise programme, as our Phase III exercise programme would not have been sufficiently challenging for them so we did not recall them for a follow-up exercise test. Details of the reasons for not having an exit fitness test are shown in Table 10:3.



**Table 10:3 Reasons behind missing exit exercise test data**

Reasons	Frequency	Percentage
Completed the programme but exit exercise test was not comparable to the first one for the following reasons:	656	49.8
Taken to different heart rate	481	73.3
Different $\beta$ blocker dose	97	14.8
Different test protocol	39	5.9
Not a standardised protocol	23	3.5
Not possible to retest	5	0.76
Glyceryl trinitrate used before treadmill	3	0.46
Retested elsewhere	1	0.15
Straight to Phase IV	4	0.61
Transferred to another centre	3	0.46
Total	656	100
Elected not to complete the CR programme	245	18.6
Underwent cardiac surgery	146	11.1
Became too ill to continue exercise programme	128	9.73
Died	35	2.66
Moved away, without a transfer	15	1.14
Came once only, to initial assessment	66	5.02
No transport available for second test	6	0.46
Refused a second test	7	0.53
At work and unable to return for second test	12	0.91
<b>Total</b>	<b>1316</b>	<b>100</b>

**10.3 Characteristics of the study cohort**

Table 10:4 shows the demographic, lifestyle and baseline clinical data for the participants who completed an exercise test at the start of CR, broken down by gender. The mean age of the cohort was 62 years. The females were significantly older than the males, with a mean age of 65. One reason for the age difference may be because females tend to be protected from developing overt coronary disease until the menopause. The majority of

study participants were male [79.8%]. The most common reason for referral to CR was following a myocardial infarction, with over half [53.5%] of participants in this category. The second main reason for referral to CR was after coronary artery bypass graft surgery. Angioplasty had only become more widely available later on in the study period. Just over 13% had undergone angioplasty procedures, some at the same time as the index cardiac event, and others electively.

Almost 9% of participants reported current smoking, a further 30% had given up within the previous year, and 30% had never smoked. Over 70% of the participants were free from co-morbid conditions, and less than 2% had reported severe co-morbid pathology. The majority [64%] felt that they had an adequate level of social support, with only 2.2% stating they had no social support at all.

A total of 1,552 participants had a body mass index measurement. The median body mass index of males was 26.8kg/m<sup>2</sup> and females 27.2kg/m<sup>2</sup>. The females were less fit than the males with a median VO<sub>2</sub> of 14.0ml/kg/min compared to the males at 20.2ml/kg/min. They also had higher median anxiety scores of 7 and depression scores of 4 than the males whose median anxiety scores were 6 and depression scores 3.



Table 10:4 Demographic, lifestyle and baseline clinical data for participants

	Male		Female		Total
	N	Mean (sd)	N	Mean (sd)	
Age, years	2167	61.0 (9.94)	547	64.7 (9.39)	2714 61.8 (9.94)
Systolic blood pressure, mmHg	2154	137 (25.0)	545	147 (27.8)	2699 139 (25.9)
Diastolic blood pressure, mmHg	2146	79.3 (12.8)	542	79.2 (12.7)	2688 79.4 (12.8)
Referrals to CR		Percentage		Percentage	Percentage
Patients who completed CR	1663	76.7	391	71.5	2054 75.7
Patients who did not complete CR	504	23.3	156	28.5	660 24.3
Total	2167	100	547	100	2714 100
Diagnostic category					
Myocardial Infarction (MI)	1150	53.1	301	55	1451 53.5
Coronary Artery Bypass Grafts	560	25.8	129	23.9	689 25.4
PCI (Angioplasty)	199	9.18	52	9.51	251 9.25
Angina Pectoris	133	6.14	36	6.58	169 6.23
Other coronary heart disease pathology	46	2.12	8	1.46	54 1.99
MI + PCI	79	3.65	21	3.84	100 3.68
Total	2167	100	547	100	2714 100

		Male		Female		Total
		Percentage		Percentage		Percentage
Reported family history of CHD		940	43.4	272	49.7	1212 44.7
Smoking history						
Non-smoker (never)		575	26.6	238	43.5	813 30
Not for >10 years		644	29.8	95	17.4	739 27.3
Not for between 1-10 years		90	4.16	16	2.93	106 3.91
Recent quitter < 1 year		663	30.6	155	28.3	818 30.2
Current smoker		192	8.87	43	7.86	235 8.67
Total		2164	100	547	100	2711 100
Reported previous history of diabetes		259	12	82	15	341 12.6
On full secondary prevention medication		432	19.9	96	17.6	528 19.5
Co-morbidity score						
None		1552	71.6	357	65.3	1909 70.3
1 (least)		252	11.6	67	12.3	319 11.8
2		293	13.5	104	19	397 14.6
3		44	2.03	13	2.38	57 2.1
4 (most)		26	1.2	6	1.1	32 1.18
Total		2167	100	547	100	2714 100



		Male		Female		Total
		Percentage		Percentage		Percentage
<b>Occupational Code 1-9</b>						
Managers & Senior officials	381	18.3	21	6.12	402	16.6
Professional occupations	233	11.2	22	6.41	255	10.5
Associate professional	210	10.1	41	12	251	10.4
Administrative & secretarial	175	8.42	107	31.2	282	11.7
Skilled trade	562	27.1	20	5.83	582	24
Personal service	36	1.73	40	11.7	76	3.14
Sales & customer	41	1.97	29	8.45	70	2.89
Process, plant and machines	274	13.2	19	5.54	293	12.1
Elementary occupations	166	7.99	44	12.8	210	8.67
<b>Total</b>	<b>2078</b>	<b>100</b>	<b>343</b>	<b>100</b>	<b>2421</b>	<b>100</b>
<b>Perception of level of social support</b>						
Yes, as much as I wanted	1001	65.7	259	57.6	1240	64
Yes, quite a bit	292	19.2	86	20.7	378	19.5
Yes, some	119	7.81	52	12.5	171	8.82
Yes, a little	76	4.99	32	7.71	108	5.57
No, not at all	36	2.36	6	1.45	42	2.17
<b>Total</b>	<b>1524</b>	<b>100</b>	<b>415</b>	<b>100</b>	<b>1939</b>	<b>100</b>

	Male		Female		Total	
		Median (10 <sup>th</sup> ,90 <sup>th</sup> percentiles)		Median (10 <sup>th</sup> ,90 <sup>th</sup> percentiles)		Median (10 <sup>th</sup> ,90 <sup>th</sup> percentiles)
Weight, kg*	2150	80.0 (67.0, 100)	544	68.0 (53.5, 90.0)	2694	79.0 (62.5, 99.0)
Body mass index, kg/m <sup>2</sup>	1217	26.8 (22.9, 32.7)	335	27.2 (22.0, 35.1)	1552	26.8 (22.7, 33.0)
Estimated VO <sub>2</sub> ml/kg/min	2167	20.2 (11.5, 29.7)	547	14.0 (7.6, 22.6)	2714	19.0 (10.2, 28.8)
Depression score	2097	3.0 (1.0, 8.0)	528	4.0 (1.0, 9.0)	2625	3.0 (1.0, 9.0)
Anxiety score	2097	6.0 (1.0, 11.0)	528	7.0 (2.0, 13.0)	2625	6.0 (1.0, 12.0)
Cholesterol mmol/L	1741	4.9 (3.6, 6.5)	436	5.2 (4.1, 7.0)	2177	4.9 (3.6, 6.7)
Fasting triglycerides mmol/L	1535	1.43 (0.79, 2.93)	392	1.56 (0.85, 2.75)	1927	1.44 (0.8, 2.9)
Index of Multiple Deprivation score	2071	6.5 (2.81, 17.4)	529	7.85 (2.95, 18.7)	2600	6.71 (2.86, 18.4)

\* Weight and body mass index have been included, but not height, since data on body mass indices are not available for all participants in the cohort



Table 10:5 shows outcome measurements for the cohort at the end of the CR programme together with changes in the same measurements, when data was available for both before and after measures, since the start of CR. All changes were significant ( $p < 0.001$ ). Mean systolic and diastolic blood pressure were significantly higher at the end of CR than at the start, which was hard to explain, since the expectation would be that with increasing fitness the systolic blood pressure would fall. However, anxiety and depression scores had significantly decreased by the end of CR. Depression scores decreased by a median value of 1 (-5.00, 1.00), which translated into an improvement of 33%. The estimated  $\text{VO}_2$  increased by a median value of 3.20, which translated into a significant improvement in fitness of 16.8% between the start and end of CR. It was interesting that participants' perception of their level of social support had risen significantly by the end of CR. Weight and body mass indices between baseline measures and completion of CR had also decreased.

I categorised participants' estimated  $\text{VO}_2$  values at the start of their CR programme into the 3 groups of low, medium or high fitness. Table 10.8 shows characteristics of the participants within these three fitness categories. There were only three variables, diastolic blood pressure, anxiety score and fasting trygliceride level, where the differences between the fitness categories did not reach significance. The mean age of the participants in the low fitness category [67.7 years] was greater than those in the high

Table 10:5 Outcomes at the end of cardiac rehabilitation and changes from baseline assessment to outcome for participants

	Outcome at end of cardiac rehabilitation			Change from baseline assessment to outcome at end of cardiac rehabilitation		
	N	Mean (sd)	N	Mean (sd)	95% Confidence Intervals	p value
Systolic blood pressure, mmHg	1972	141 (24.5)	1967	1.77 (21.7)	0.81,2.73	<0.001 <sup>a</sup>
Diastolic blood pressure, mmHg	1951	81.1 (12.4)	1944	1.65 (13.1)	1.06,2.23	<0.001 <sup>a</sup>
		Median (10 <sup>th</sup> , 90 <sup>th</sup> percentiles)		(Median, 10 <sup>th</sup> , 90 <sup>th</sup> percentiles)		
Weight, kg <sup>a</sup>	1915	78.5 (63.5, 98.0)	1913	0.00 (-4.00, 3.50)	-0.46,-0.15	<0.001 <sup>a</sup>
Body mass index, kg/m <sup>2</sup>	1109	26.6 (22.8, 32.4)	1108	-0.18 (-1.48, 1.10)	-0.28,-0.15	<0.001 <sup>a</sup>
Estimated VO <sub>2</sub> ml/kg/min	1401	24.5 (14.0, 35.0)	1398	3.20 (0.00, 8.10)	3.60,3.95	<0.001 <sup>a</sup>
Depression score	1965	2.00 (0.00, 6.00)	1939	-1.00 (-5.00, 1.00)	-1.45,-1.22	<0.001 <sup>a</sup>
Anxiety score	1966	4.00 (1.00, 9.00)	1940	-1.00 (-5.00, 2.00)	-1.37,-1.10	<0.001 <sup>a</sup>
Perception of level of social support	1440	1.00 (1.00, 3.00)	1421	0.00 (-1.00, 1.00)	-0.17,-0.07	<0.001 <sup>a</sup>

<sup>a</sup> T test

<sup>a</sup>Weight and body mass index have been included, but not height, since data on body mass indices are not available for all participants in the cohort



fitness category [56.7 years]. Men were significantly more likely to be in the high fitness category compared to women. The fitter participants had significantly lower systolic blood pressures, a lower body mass index, were less likely to be suffering from depression, had little or no concomitant co-morbidity, and were more likely to be living in a more affluent part of Hampshire ( $p<0.001$ ).

The fitter participants were more likely to complete CR than the less fit [Table 10:6]. Eighty-two per cent of those in the high fitness category completed the programme compared with 66% in the low fitness category. The fittest participants were also more likely to have been referred to CR following revascularisation procedures with the highest proportion of participants who had undergone angioplasty being in the high fitness groups.

**Table 10:6 Percentage of participants who completed or did not complete cardiac rehabilitation by fitness level at baseline**

Referrals to CR	Baseline Fitness Level		
	Low n = 501	Medium n = 778	High n = 775
Participants who completed CR	65.8%	76.8%	82.4%
	Low n = 260	Medium n = 234	High n = 166
Participants who did not complete CR	34.2%	23.1%	17.6%

(Chi square test  $p < 0.001$ )

Those who said they have as much social support as they wanted were most predominant in the high fitness group whereas conversely those who thought they lacked social support tended to be in the low fitness category.

There were recorded measures of baseline depression for 2,625 out of the 2,714 participants in the cohort. Of these, 122 [4.64%] were found to score greater than 10 on the HADS, suggestive of clinical depression, with 274 [10.6%] of the remaining participants in the borderline depression group [score of 8-10]. The majority [84.3%] of participants were not depressed at baseline. However, considerably more females (16.5%) than males (8.92%) were in the borderline depression group. More females (5.68%) were in the group with symptoms suggestive of clinical depression than males (4.39%). Those with clinical depression were less likely to complete the CR programme than those who were not depressed. Forty-two per cent of those in the clinically depressed category failed to finish CR compared with 21.7% of the non-depressed [Table 10:7].

**Table 10:7 Percentage of participants who completed or did not complete cardiac rehabilitation by depression category at baseline**

Referrals to CR	Baseline HADS Depression score		
	score 11-21 suggests clinical depression n = 71	score 8-10 possible borderline symptoms n = 191	score 0-7 no depression n = 1746
Participants who completed CR	58.2%	69.7%	78.3%
	n = 51	n = 83	n = 483
Participants who did not complete CR	41.8%	30.3%	21.7%

(Chi square test p < 0.001)



The depression score values from the HADS were used to categorise the participants into three groups; those with no symptoms of depression [0-<8], those exhibiting signs of borderline depression [8-10] and those whose symptoms indicate clinical depression [>10]. Table 10:9 shows the various characteristics of the participants within the three depression categories. In contrast to the previous table [Table 10:8] where most of the variables had shown a significant association with the levels of fitness, most variables were not significantly related to depression. The exceptions to this were being female, failing to complete the CR programme, being a current or recent smoker, having concomitant co-morbid illness, perceiving a lack of social support and being unfit ( $p<0.001$ ).

The clinically depressed group contained proportionally more current smokers and recent quitters. Sixteen per cent of them reported current smoking on the first assessment at CR, compared with 7.9% in the group who were not depressed.

Of the proportion of participants with and without co-morbidity within the three depression groups, those with no co-morbidity [71.5% versus 64.8%] were more predominant in the group who were not depressed and those with high co-morbidity scores were more predominant in the clinically depressed group [2.46% versus 1.08%]. The participants who stated that they had as much

social support as they needed were in the majority [67.6%] and did not report depressive symptoms. This was in contrast to those who felt they had little social support and was found predominantly in the groups with borderline or clinical depression.



Table 10:8 Characteristics of study participants in relation to estimated levels of fitness at baseline

	Low fitness level		Medium fitness level		High fitness level		Total		p value
	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)	
Age, years	761	67.7 (8.67)	1012	62.1 (8.88)	941	56.7(9.21)	2714	61.8(9.94)	<0.001 <sup>c</sup>
Systolic blood pressure, mmHg	753	145 (28.5)	1009	139 (25.4)	937	133 (22.8)	2699	138 (25.9)	<0.001 <sup>c</sup>
Diastolic blood pressure, mmHg	749	79.8 (13.5)	1005	79.0 (12.6)	934	79.4 (12.5)	2689	79.4 (12.8)	0.036 <sup>c</sup>
Gender									
Male	447	20.6	837	38.6	883	40.8	2167	100	<0.001 <sup>b</sup>
Female	314	57.4	175	32.0	58	10.6	547	100	
Referrals to CR									<0.001 <sup>b</sup>
Patients who completed CR	501	65.8	778	76.8	775	82.4	2054	75.7	
Patients who did not complete CR	260	34.2	234	23.1	166	17.6	660	24.3	
Diagnostic category									<0.001 <sup>b</sup>
Myocardial Infarction (MI)	439	57.7	542	53.6	470	50.0	1451	53.5	
Coronary Artery Bypass Grafts	205	26.9	283	28	210	21.4	689	25.4	
PCI (Angioplasty)	39	5.12	70	6.92	142	15.1	251	9.25	
Angina Pectoris	41	5.39	72	7.11	56	5.95	169	6.23	
Other coronary heart disease pathology	17	2.23	21	2.08	16	1.70	54	1.99	
MI+PCI	20	2.63	24	2.37	56	5.95	100	3.68	

<sup>a</sup>ANOVA test-bonferroni

<sup>b</sup>Chi square test

	Low fitness level				Medium fitness level				High fitness level				Total	p value	
	N	Percentage	N	Percentage	N	Percentage	N	Percentage	N	Percentage					
Reported family history of CHD	309	40.6	434	42.9	469	49.8	1212	44.7	<0.001 <sup>b</sup>						
	Smoking history														
	Never	258	34	267	26.4	288	30.6	813	30	<0.001 <sup>b</sup>					
	Not for >10 years	225	29.6	290	28.7	224	23.8	739	27.3	<0.001 <sup>b</sup>					
	Not for between 1-10 years	27	3.55	43	4.25	36	3.83	106	3.91	<0.001 <sup>b</sup>					
	Recent quitter < 1 year	204	26.8	319	31.6	295	31.4	818	30.2	<0.001 <sup>b</sup>					
	Current smoker	46	6.05	92	9.1	97	10.3	235	8.67	<0.001 <sup>b</sup>					
	Reported previous history of diabetes														
	152	20	116	11.5	73	7.76	341	12.6	<0.001 <sup>b</sup>						
	On full secondary prevention medication														
134	17.6	163	16.1	231	24.6	528	19.5	<0.001 <sup>f</sup>							
Co-morbidity score															
None	440	57.8	719	71.1	750	79.7	1909	70.3	<0.001 <sup>f</sup>						
1 (least)	107	14.1	118	11.7	94	9.99	319	11.8	<0.001 <sup>f</sup>						
2	161	21.2	149	14.7	87	9.25	397	14.6	<0.001 <sup>f</sup>						
3	38	4.99	13	1.28	6	0.64	57	2.1	<0.001 <sup>f</sup>						
4 (most)	15	1.97	13	1.28	4	0.43	32	1.18	<0.001 <sup>f</sup>						
Jonckheere-Terpstra															
Chi square test															



	Low fitness level				Medium fitness level				High fitness level				Total	p value
	N	Percentage	N	Percentage	N	Percentage	N	Percentage	N	Percentage	N	Percentage		
Occupational Code 1-9	Managers & Senior officials	72	12.1	136	14.8	194	21.4	402	16.6				<0.001 <sup>b</sup>	
	Professional occupations	61	10.3	99	10.8	95	10.5	255	10.5					
	Associate professional	60	10.1	90	9.8	101	11.1	251	10.4					
	Administrative & secretarial	92	15.5	105	11.4	85	9.36	282	11.7					
	Skilled trade	142	23.9	216	23.5	224	24.7	582	24					
	Personal service	28	4.71	31	3.38	17	1.87	76	3.14					
	Sales & customer	25	4.2	26	2.83	19	2.09	70	2.89					
	Process, plants & machinery	60	10.1	135	14.7	98	10.8	293	12.1					
	Elementary occupation	55	9.24	80	8.71	75	8.26	210	8.67					
	Perception of level of social support	Yes, as much as I wanted	330	56.2	411	66.6	499	67.9	1240	64				
Yes, quite a bit		126	21.5	105	17	147	20	378	19.5					
Yes, some		68	11.6	56	9.08	47	6.39	171	8.82					
Yes, a little		42	7.16	36	5.83	30	4.08	108	5.57					
No, not at all		21	3.58	9	1.46	12	1.63	42	2.17					
Jonckheere-Terpstra														
Chi square test														

	Low fitness level			Medium fitness level			High fitness level			Total	p value
	N	Median (10 <sup>th</sup> , 90 <sup>th</sup> percentiles)		N	Median (10 <sup>th</sup> , 90 <sup>th</sup> percentiles)		N	Median (10 <sup>th</sup> , 90 <sup>th</sup> percentiles)			
Weight, kg	754	76.3 (60.0, 101)		1005	79.5 (63.0, 99.0)		935	80.0 (65.0, 97.0)		2694	79.0 (62.5, 99.0)
Body mass index, kg/m <sup>2</sup>	456	27.6 (23.1, 35.3)		510	27.0 (23.0, 33.2)		586	26.2 (22.3, 31.6)		1552	26.8 (22.7, 33.0)
Depression score	725	4.00 (1.00, 9.00)		981	3.00, (1.00, 9.00)		919	2.00 (0.00, 8.00)		2625	3.00 (1.00, 9.00)
Cholesterol mmol/L	592	4.90 (3.70, 6.90)		814	5.10 (3.70, 6.70)		771	4.80 (3.60, 6.30)		2177	4.9 (3.6, 6.7)
Fasting triglycerides mmol/L	540	1.53 (0.82, 2.74)		697	1.43 (0.80, 2.92)		690	1.40, (0.79, 2.94)		1927	1.44 (0.80, 2.90)
Index of Multiple Deprivation score	736	8.00 (3.24, 18.7)		969	6.55 (2.86, 18.4)		895	6.05 (2.17, 15.5)		2600	6.71 (2.86, 18.4)

<sup>a</sup>Kruskal-Wallis  
Low fitness = estimated VO<sub>2</sub> below 15ml/O<sub>2</sub>/kg

Medium fitness = estimated VO<sub>2</sub> between 15-22ml/O<sub>2</sub>/kg

High fitness = estimated VO<sub>2</sub> above 22ml/O<sub>2</sub>/kg



Table 10:9 Characteristics of study participants who completed a fitness test in relation to levels of depression at baseline

	No depression		Borderline depression		Clinical depression		Total	p value
	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)	Mean (sd)	
Age, years	2278	62.1 (10.0)	286	62.6 (10.6)	138	60.4 (10.9)	62.0 (10.1)	0.465 <sup>a</sup>
Systolic blood pressure, mmHg	2221	139 (25.8)	274	138 (27.0)	120	134 (25.1)	139 (25.9)	0.564 <sup>a</sup>
Diastolic blood pressure, mmHg	2217	79.5 (12.8)	272	78.4 (13.3)	119	78.3 (10.3)	79.3 (12.8)	0.005 <sup>a</sup>
Gender				Percentage		Percentage	Percentage	
Male	1818	86.7	187	8.92	92	4.39	100	<0.001 <sup>b</sup>
Female	411	77.8	87	16.5	30	5.68	100	
Referrals to CR								
Patients who completed CR	1746	78.3	191	69.7	71	58.2	76.5	<0.001 <sup>b</sup>
Patients who did not complete CR	483	21.7	83	30.3	51	41.8	23.5	
Diagnostic category								0.263 <sup>b</sup>
Myocardial Infarction (MI)	1190	53.4	156	56.9	63	51.6	53.7	
Coronary Artery Bypass Grafts	573	25.7	61	22.3	33	27.1	25.4	
PCI (Angioplasty)	213	9.56	17	6.20	9	7.38	9.10	
Angina Pectoris	132	5.92	21	7.66	12	9.84	6.29	
Other coronary heart disease pathology	35	1.57	8	2.92	2	1.64	1.71	
MI+PCI	86	3.86	11	4.01	3	2.46	3.81	

<sup>a</sup>ANOVA test-bonferroni

<sup>b</sup>Chi square test

	No depression	Borderline depression	Clinical depression	Total	p value
Reported family history of CHD	N 992	N 135	N 54	N 1181	Percentage 45.0
Smoking history					<0.001 <sup>b</sup>
Never	671	67	38	776	29.6
Not for >10 years	627	74	17	718	27.4
Not for between 1-10 years	91	9	3	103	3.93
Recent quitter < 1 year	663	92	44	799	30.5
Current smoker	176	32	20	228	8.69
Reported previous history of diabetes	274	40	18	332	12.7
On full secondary prevention medication	438	65	13	516	19.7
Co-morbidity score					<0.001 <sup>b</sup>
None	1594	166	79	1839	70.1
1 (least)	259	39	15	313	11.9
2	312	57	18	387	14.7
3	40	8	7	55	2.10
4 (most)	24	4	3	31	1.18

<sup>a</sup>Mann Whitney U test



	No depression				Borderline depression				Clinical depression				Total				p value
	N		Percentage		N		Percentage		N		Percentage		N		Percentage		
Occupational Code 1-9	Managers & Senior officials		333		16.6		37		20		18.2		390		16.6		
	Professional occupations		216		10.8		17		11		10.0		244		10.4		
	Associate professional		219		10.9		16		10		9.09		245		10.4		
	Administrative & secretarial		227		11.3		34		11		10.0		272		11.6		
	Skilled trade		495		24.7		50		22		22.0		567		24.2		
	Personal service		63		3.14		8		4		4.64		75		3.20		
	Sales & customer		53		2.64		11		4		3.64		68		2.90		
	Process, plants & machinery		232		11.6		34		17		15.5		283		12.1		
	Elementary occupation		169		8.42		23		11		10.0		203		8.65		
	Perception of level of social support		1105		67.6		101		30		34.1		1236		63.9		
<0.001 <sup>c</sup>	Yes, as much as I wanted		299		18.3		62		26		29.6		377		19.5		
	Yes, some		134		8.20		24		13		14.8		171		8.85		
	Yes, a little		66		4.04		27		15		14.1		108		5.59		
	No, not at all		30		1.84		7		4		4.55		41		2.12		
	Chi square test																

	No depression	Borderline depression	Clinical depression	Total	p value
Weight, kg*	Median (10 <sup>th</sup> , 90 <sup>th</sup> percentiles) N	Median (10 <sup>th</sup> , 90 <sup>th</sup> percentiles) N	Median (10 <sup>th</sup> , 90 <sup>th</sup> percentiles) N	Median (10 <sup>th</sup> , 90 <sup>th</sup> percentiles) N	
Body mass index, kg/m <sup>2</sup>	1297 26.8 (22.7, 32.7)	161 26.7 (23.3, 34.6)	58 28.1 (22.4, 34.5)	1516 26.8 (22.7, 33.0)	0.335 §
Estimated VO <sub>2</sub> mL/kg/min	2229 19.2 (10.5, 29.2)	274 17.5 (8.2, 27.2)	122 16.6 (7.00, 26.8)	2625 19.1 (10.2, 28.9)	<0.001 §
Cholesterol mmol/L	1831 4.90 (3.60, 6.80)	213 5.00 (3.60, 6.80)	90 5.10 (3.75, 6.55)	2134 4.90 (3.60, 6.60)	0.932 §
Fasting triglycerides mmol/L	1623 1.43 (0.79, 2.78)	195 1.55 (0.85, 3.24)	76 1.42 (0.79, 3.00)	1894 1.44 (0.80, 2.87)	0.020 §
Index of Multiple Deprivation score	2128 6.50 (2.77, 17.5)	269 8.64 (3.03, 18.4)	118 7.67 (2.95, 18.7)	2515 6.71 (2.85, 18.4)	0.010 §

\*Weight and body mass index have been included, but not height, since data on body mass indices are not available for all participants in the cohort

Not depressed = score of 0-7      Borderline depression = score 8-10      Clinically depressed = 11-21



Fitness levels were related to depression scores and the participants in the clinically depressed group were less fit than their non-depressed counterparts ( $p<0.001$ ) as shown in Table 10:10. The median estimated  $VO_2$  for those reported to be depressed was 16.6ml/kg/min compared with 17.5ml/kg/min for those who had borderline depression and 19.2ml/kg/min for those with no depression.

**Table 10:10 Depression scores of participants at baseline related to fitness category**

<b>HADS Depression score</b>	<b>Low fitness n = 725</b>	<b>Medium fitness n = 981</b>	<b>High fitness n = 919</b>
Score 0 -7 No depression	78.3%	86.1%	88.8%
Score 8-10 possible borderline symptoms	14.6%	9.89%	7.73%
Score 11-21 suggests clinical depression	7.03%	3.98%	3.48%

(Chi square test  $p < 0.001$ )

Having looked at the baseline characteristics of the cohort in relation to both fitness and depression as categorical variables, I then examined the changes in fitness and depression between initial assessments at the start of CR and the outcome assessment at the end of CR with the data that was available [Table 10:11] and compared the numbers of participants in each category of fitness or depression at baseline and at the finish of CR [Tables 10:12 and 10:13].

**Table 10:11 Median fitness and depression scores before and after cardiac rehabilitation**

	Before Cardiac rehabilitation	After Cardiac rehabilitation	p value
Median estimated VO <sub>2</sub> score (10 <sup>th</sup> , 90 <sup>th</sup> percentiles)	19.1 (10.2,28.8)	24.5 (14.0,35.0)	<0.001 <sup>b</sup>
Median HADS score (10 <sup>th</sup> , 90 <sup>th</sup> percentiles)	3.00 (1.00,9.00)	2.00 (0.00,6.00)	<0.001 <sup>b</sup>

(<sup>b</sup>Chi square test )

**Table 10:12 Change in fitness category before and after cardiac rehabilitation**

VO <sub>2</sub> Category BEFORE		VO <sub>2</sub> category AFTER		
	Total	High Fitness	Medium fitness	Low fitness
High fitness	535	529	6	0
Medium fitness	539	295	238	6
Low fitness	324	20	151	153
Total participants	1398	844	395	159

(Chi square test p < 0.001)

At the end of the Phase III CR programme nearly half of the 324 participants from the low fitness group [151] had moved into the medium group and 20 participants into the high group. Similarly, just over half of those in the medium fitness group [295/539] moved to the high fitness group and very few participants had dropped into a lower fitness category.



**Table 10:13 Change in depression category before and after cardiac rehabilitation**

HADS Depression Score BEFORE		HADS Depression Score AFTER		
	Total	Score 0 - 7	Score 8 - 10	Score 11-21
Score 0 - 7 no depression	1690	1658	28	4
Score 8 – 10 possible borderline symptoms	182	152	21	9
Score 11-21 suggests clinical depression	67	44	14	9
Total participants	1939	1854	63	22

(Chi square test p < 0.001)

There were 67 participants with documented changes in depression scores recorded from initial and final assessments whose scores indicated symptoms of clinical depression. By the end of the programme nearly three-quarters of these [44] moved into the ‘No depression’ category, 14 moved into the borderline depression category. There were 22 in the clinically depressed category; 9 patients who had been depressed at baseline and 13 patients who had become clinically depressed between the start and end of the programme.

Table 10:14 shows the change in fitness and depression categories between the start and end of the programme.

**Table 10:14 Change in fitness and depression categories before and after cardiac rehabilitation**

	Improved	Deteriorated	p value
Fitness Category	33.3% n = 466/1398	0.86% n = 12/1398	<0.001 <sup>b</sup>
Depression Category	10.7% n = 210/1939	2.10% n = 41/1939	<0.001 <sup>b</sup>

<sup>b</sup>Chi square test

Out of 1.398 participants with change in fitness data, 33% improved their fitness category compared to less than 1% who deteriorated [Table 10:14]. For depression scores, 10.7% of participants showed an improvement compared with 2.1% who deteriorated [Table 10:14].



# Chapter 11

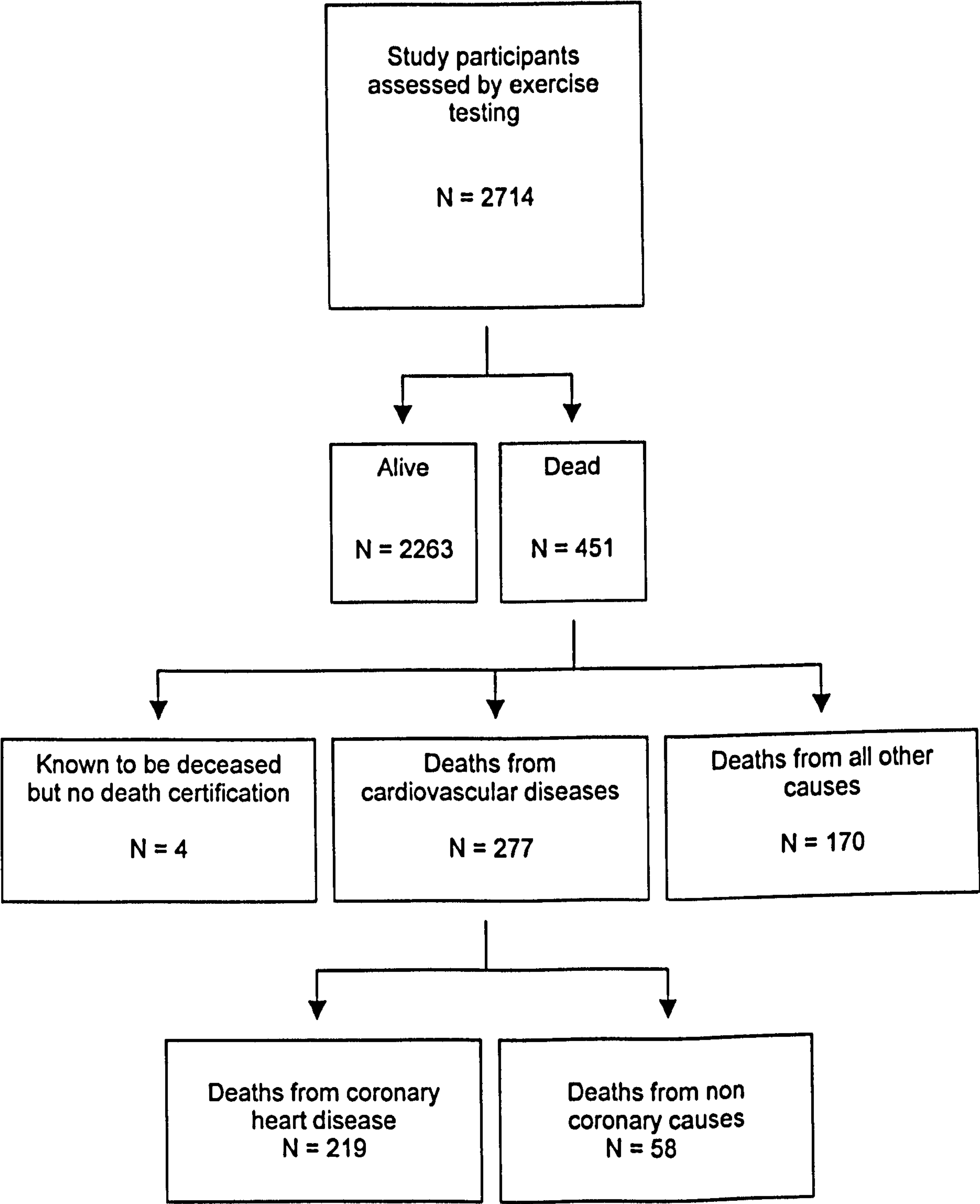
## Results from Survival Analyses

### ***11.1 Survival analyses***

Survival data requires methods of analysis that accommodate the presence of censored observations and staggered entry of participants into a study. The observational period was calculated from the time the participant began CR up to 15<sup>th</sup> November 2005 or death if earlier.

I had available almost 13 years, median 6.4 years, of follow-up, and the cause of death by three categories: all-cause deaths, cardiovascular deaths and deaths specifically from coronary heart disease [Figure 11:1]. A total of 451 participants had died which represents 16.6% of the cohort, [16.8% of males and 16.1% of females]. There were 277 deaths from cardiovascular causes [10.2% of the cohort] and 170 [6.3%] from other causes, mainly cancers. As expected, 219 [79.1%] of the cardiovascular deaths were from coronary heart disease [Figure 11:1 and Table 8:7].

**Figure 11:1 Flow chart of survival outcomes for the study participants**



There was a total of 18,000 person years of follow-up. Table 11:1 shows the all cause death rate per 1000 person years, Table 11:2 shows the cardiovascular death rate and Table 11:3 the cardiovascular death rate by gender both in the same period.



**Table 11:1 All-cause death rate per 1000 person years**

Cohort	Person years	Deaths	Rate per 1000 person years	95% Confidence Interval
<b>Gender</b>				
Male	14439	363	25.1	22.7, 27.9
Female	3561	88	24.7	20.1, 30.5
<b>Total</b>	<b>18000</b>	<b>451</b>	<b>25.1</b>	<b>22.8, 27.5</b>
<b>Age in 10 year bands</b>				
<50 years	2565	18	7.02	4.42, 11.1
50-59 years	5205	91	17.5	14.2, 21.5
60-69 years	6620	150	22.7	19.3, 26.6
70+ years	3611	192	53.2	46.2, 61.3

**Table 11:2 Cardiovascular death rate per 1000 person years**

Cohort	Person years	Deaths	Rate per 1000 person years	95% Confidence Interval
<b>Gender</b>				
Male	14439	224	15.5	13.6, 17.8
Female	3561	53	14.9	11.4, 19.5
<b>Total</b>	<b>18000</b>	<b>277</b>	<b>15.4</b>	<b>13.7, 17.3</b>
<b>Age in 10 year bands</b>				
<50 years	2565	14	5.46	3.23, 9.25
50-59 years	5205	53	10.2	7.79, 13.4
60-69 years	6620	95	14.4	11.7, 17.5
70+ years	3611	115	31.9	26.5, 38.2

**Table 11:3 Cardiovascular death rate per 1000 person years, by gender**

Cohort	Person years	Deaths	Rate per 1000 person years	95% Confidence Interval
<b>Males</b>				
<b>Age in 10 year bands</b>				
<50 years	2265	11	4.86	2.69, 8.77
50-59 years	4477	49	10.9	8.27, 14.5
60-69 years	5162	74	14.3	11.4, 18.0
70+ years	2535	90	35.5	28.9, 43.6
<b>Total</b>	<b>14439</b>	<b>224</b>	<b>15.5</b>	<b>13.3, 17.7</b>
<b>Females</b>				
<b>Age in 10 year bands</b>				
<50 years	300	3	10.0	3.32, 31.0
50-59 years	728	4	5.50	2.06, 14.6
60-69 years	1458	21	14.4	9.39, 22.1
70+ years	1075	25	23.3	15.7, 34.4
<b>Total</b>	<b>3561</b>	<b>53</b>	<b>14.9</b>	<b>11.4, 19.5</b>

Low fitness shows an effect on survival. This is illustrated in the Kaplan-Meier graph comparing survival times by categories of baseline fitness [Figure 11:2]. Depression scores of greater than 10 at baseline indicate a small effect on survival. At this stage, however, I had not considered the effect of confounding on these results.



Figure 11:2 Kaplan-Meier survival estimates for baseline fitness

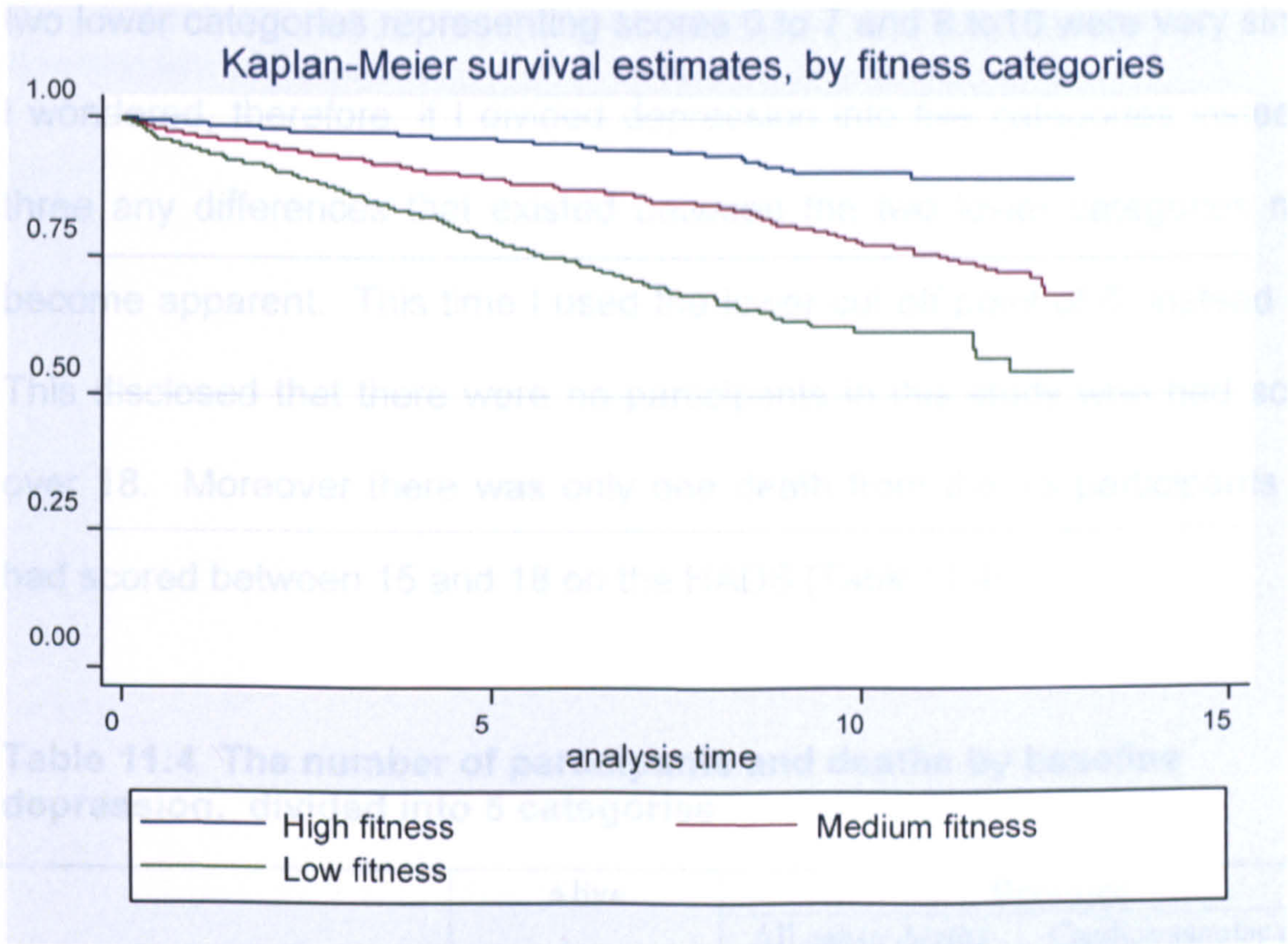


Figure 11:3 Kaplan-Meier survival estimates for baseline depression

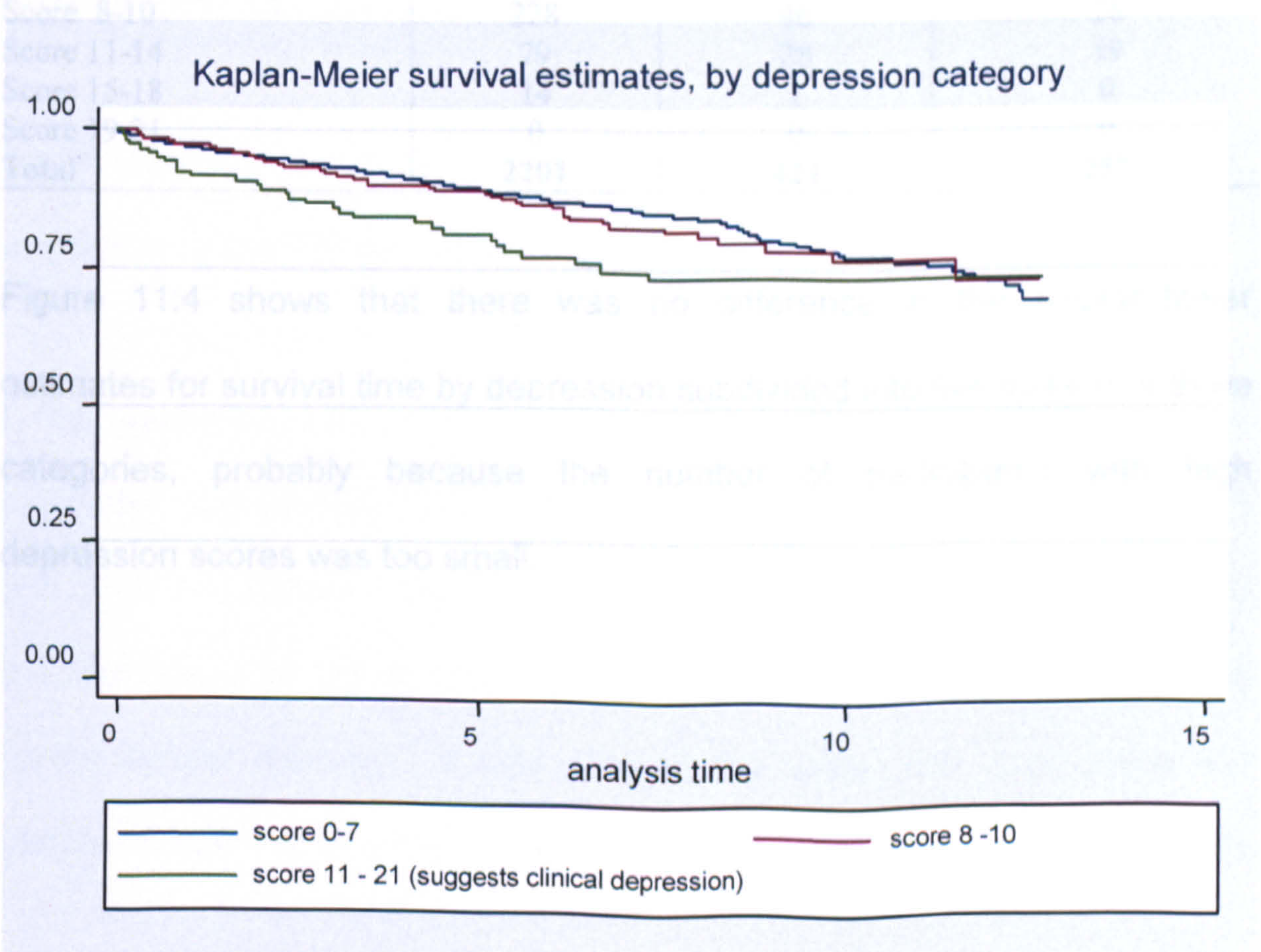




Figure 11:3 shows the effect of baseline depression scores on survival. The two lower categories representing scores 0 to 7 and 8 to10 were very similar. I wondered, therefore, if I divided depression into five categories instead of three any differences that existed between the two lower categories might become apparent. This time I used the lower cut off point of 6, instead of 7. This disclosed that there were no participants in this study who had scored over 18. Moreover there was only one death from the 15 participants who had scored between 15 and 18 on the HADS [Table11:4].

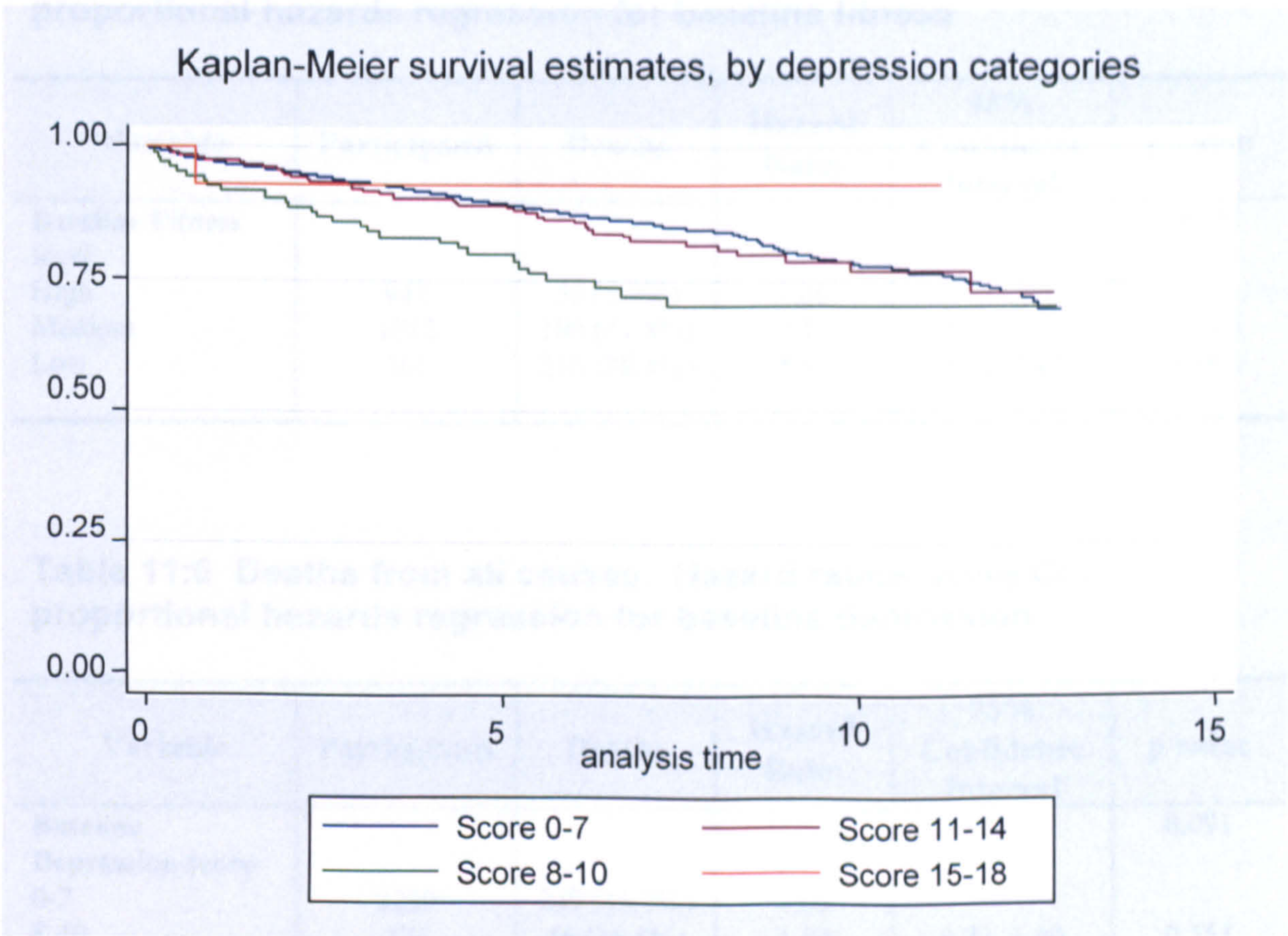
**Table 11:4 The number of participants and deaths by baseline depression, divided into 5 categories**

	Alive	Deceased	
		All cause deaths	Cardiovascular deaths
<b>Baseline Depression level</b>			
Score 0-7	1880	349	212
Score 8-10	228	46	26
Score 11-14	79	28	19
Score 15-18	14	1	0
Score 19-21	0	0	0
<b>Total</b>	<b>2201</b>	<b>424</b>	<b>257</b>

Figure 11:4 shows that there was no difference in the Kaplan-Meier estimates for survival time by depression subdivided into five instead of three categories, probably because the number of participants with high depression scores was too small.



**Figure 11:4 Kaplan-Meier survival estimates, by 5 categories of depression at baseline**



For all subsequent analyses, I consider firstly the 451 deaths from all causes, and secondly the 277 cardiovascular deaths.

I first assessed the crude estimates of the effects of baseline fitness categories and baseline HADS scores on deaths from all causes [Table 11:5 and 11:6] and cardiovascular causes [Tables 11:7 and 11:8]. This showed the importance of fitness levels ( $p<0.001$ ) in predicting both all-cause and cardiovascular mortality. It also showed the higher risk of all-cause and cardiovascular mortality for the top depression category ( $p=0.091$  for deaths



from all causes and  $p=0.130$  for cardiovascular deaths), although this association may not be linear.

**Table 11:5 Deaths from all causes. Hazard ratios using Cox proportional hazards regression for baseline fitness**

Variable	Participants	Deaths	Hazard Ratio	95% Confidence Interval	p value
Baseline Fitness level					<0.001
High	941	55 (5.4%)	1.00		
Medium	1012	180 (17.8%)	2.73	2.02, 3.69	<0.001
Low	761	216 (28.4%)	5.55	4.13, 7.47	<0.001

**Table 11:6 Deaths from all causes. Hazard ratios using Cox proportional hazards regression for baseline depression**

Variable	Participants	Deaths	Hazard Ratio	95% Confidence Interval	p value
Baseline Depression score					0.091
0-7	2229	349 (15.7%)	1.00		
8-10	274	46 (16.8%)	1.10	0.81, 1.49	0.551
11-21	122	29 (23.8%)	1.56	1.06, 2.27	0.022

**Table 11:7 Deaths from cardiovascular causes. Hazard ratios using Cox proportional hazards regression for baseline fitness**

Variable	Participants	Deaths	Hazard Ratio	95% Confidence Interval	p value
Baseline Fitness level					<0.001
High	941	24 (2.55%)	1.00		
Medium	1012	107 (10.6%)	3.77	2.42, 5.87	<0.001
Low	761	146 (19.2%)	8.53	5.54, 13.1	<0.001



**Table 11:8 Deaths from cardiovascular causes. Hazard ratios using Cox proportional hazards regression for baseline depression**

Variable	Participants	Deaths	Hazard Ratio	95% Confidence Interval	p value
Baseline Depression score					0.130
0-7	2229	212 (9.51%)	1.00		
8-10	274	26 (9.49%)	1.01	0.68, 1.53	0.925
11-21	122	19 (15.6%)	1.68	1.05, 2.69	0.030

For subsequent model analyses and after considering various methods, I chose to use the model selection method described by David Collett (Collett 1994). This allowed me to assess which variables were related to outcome and needed to be included in the model for all-cause or cardiovascular death times.

## **11.2 Strategy for model selection**

### **11.2.1 Building the model for all-cause mortality with complete data**

The process I used for building the model selection is divided into four steps. Model selection for all-cause mortality is described in detail in the following section of this chapter. I used a similar process to produce the final model for cardiovascular deaths.

#### **Step 1**

I fitted models using each variable one at a time from the clinical and demographic data as shown in Table 11:9 to determine which variables on their own had a significant effect on mortality. At this point I did not include the two exposure variables, fitness and depression as they were the focus of my research. I used a specific STATA command to ensure that only cases without missing data were included. One of my difficulties was that some variables had missing data and it was not possible to choose a model from these without losing much data. I started with the variables where there were complete data.



Table 11:9 Deaths from all causes. Hazard ratios using Cox proportional hazards regression for clinical and demographic variables, unadjusted

Variable	Participants	Deaths	Hazard Ratio	95% Confidence Interval	p value
Age, years	2714		1.07	1.06, 1.08	<0.001
Gender					0.932
Male	2167	363 (16.8%)	1		
Female	547	88 (16.1%)	0.999	0.784, 1.24	
Systolic blood pressure, mmHg	2699		1.00	1.00, 1.00	0.884
Diastolic blood pressure, mmHg	2688		0.992	0.985, 1.00	0.604
Referrals to CR					<0.001
Patients who completed CR	2054	268 (13.1%)	1		
Patients failing to complete CR	660	183 (27.7%)	2.42	2.00, 2.92	
Diagnostic category					<0.001
Myocardial infarction (MI)	1451	319 (22.0%)	1		
Coronary Artery Bypass Grafts	689	72 (10.5%)	0.511	0.395, 0.660	
PCI (Angioplasty)	251	14 (5.58%)	0.317	0.185, 0.541	
Angina Pectoris	169	28 (16.6%)	0.711	0.483, 1.046	
Other coronary heart disease pathology	54	13 (24.1%)	1.44	0.824, 2.503	
MI + PCI	100	5 (5.00%)	0.317	0.131, 0.769	

Variable	Participants	Deaths	Hazard Ratio	95% Confidence Interval	p value
<b>Family history of coronary heart disease</b>					0.001
None	1502	280 (18.6%)	1		
Some history	1212	171 (14.1%)	0.711	0.588, 0.861	
<b>Smoking history</b>					0.529
Non-smoker (never)	813	125 (15.4%)	1		
Not for > 10 years	739	127 (17.2%)	1.21	0.943, 1.55	
Not for between 1, 10 years	106	16 (15.1%)	1.19	0.71, 2.00	
Recent quitter < 1 year	818	138 (16.9%)	1.05	0.828, 1.34	
Current smoker	235	44 (18.7%)	1.24	0.878, 1.747	
<b>History of diabetes</b>					0.001
No history of diabetes	2373	380 (16.01%)	1		
Reported previous history of diabetes	341	71 (20.8%)	1.60	1.24, 2.064	
<b>Secondary prevention medication</b>					0.366
On full secondary prevention	528	52 (9.85%)	1		
Not on full secondary prevention	2186	399 (18.3%)	0.874	0.65, 1.18	
<b>Co-morbidity score</b>					<0.001
No co-morbidity	1909	270 (14.1%)	1		
1 (least)	319	63 (19.8%)	1.46	0.395, 0.660	
2	397	84 (21.2%)	1.82	0.185, 0.541	
3	57	21 (36.8%)	3.63	0.483, 1.046	
4 (most)	32	13 (40.6%)	5.6	0.824, 2.503	



Variable	Participants	Deaths	Hazard Ratio	95% Confidence Interval	p value
<b>Occupational Code 1 - 9</b>					0.724
Managers & Senior officials	402	53 (13.2%)	1		
Professional occupations	255	44 (17.3%)	1.42	0.95, 2.12	
Associate professional	251	41 (16.3%)	1.29	0.86, 1.94	
Administrative & secretarial	282	45 (16.0%)	1.24	0.83, 1.84	
Skilled trade	582	94 (16.2%)	1.27	0.92, 1.79	
Personal service	76	12 (15.8%)	1.35	0.72, 2.53	
Sales & customer	70	10 (14.3%)	1.14	0.58, 2.26	
Process, plant and machines	293	45 (15.4%)	1.19	0.80, 1.77	
Elementary occupations	210	39 (18.6%)	1.52	1.01, 2.31	
<b>Perception of level of social support</b>					0.0418
Yes, as much as I wanted	1240	132 (10.7%)	1		
Yes, quite a bit	378	49 (13.0%)	1.19	0.86, 1.65	
Yes, some	171	27 (16.0%)	1.51	0.10, 2.29	
Yes, a little	108	21 (19.4%)	1.92	1.21, 3.04	
No, not at all	42	7 (16.8%)	1.61	0.75, 3.44	
<b>Weight, kg</b>	2964		0.991	0.984, 0.996	0.0066
<b>Body mass index kg/m<sup>2</sup></b>	1552		0.98	0.94, 1.01	0.207
<b>Cholesterol mmol/L</b>	2177		1.097	1.00, 1.20	0.0419
<b>Fasting triglycerides mmol/L</b>	1927		0.98	0.87, 1.11	0.7904
<b>Index of Multiple Deprivation score</b>	2600		1.013	1.00, 1.030	0.098

## Step 2

For the second step of model selection variables, those that appeared to be important ( $p < 0.1$ ) from Step 1, were then fitted together into the model. These were age, whether the participant completed CR category, diagnosis category at referral, family history of coronary heart disease, diagnosis of diabetes and co-morbidity score. Variables that appeared important may cease to be so in the presence of other variables. I removed each variable one by one from the model and assessed the change in model fit. The variables that led to a significant increase in the log likelihood ratio were kept in the model, and the variables whose removal did not lead to significant change in model fit were eliminated. Once a variable was discarded the effect of the variables that had been retained were examined again in turn. During this process I found two variables that did not reach significance and were therefore discarded. These were family history of coronary heart disease and a diagnosis of diabetes.

## Step 3

The third step in the process was to add any variable to the model that had formerly not been considered important in Step 2. This was done to check whether the variable I had added would become important in the presence of other variables. Gender was the only variable with complete data that fitted this category. Although not originally significant at Step 1, gender reached significance in the presence of the other variables in the model and was thus retained.



#### Step 4

For the fourth and final step of the process, I re-checked to see if any of the remaining variables in the model could be discarded by repeating the process of dropping them, computing the change with the log likelihood ratio test and then reinstating each variable one at a time if the value of the log did not increase significantly. At the end of model fitting the best combination was a model that included the following variables: age, whether the participant completed CR category, diagnosis category at referral, co-morbidity score and gender. All these terms had remained significant during the model selection process [Table 11:11].

#### **11.2.2 Building the model for all-cause mortality using variables with complete and missing data**

I then considered building the model by adding the variables where data were missing data as well as the variables with complete data. I repeated steps 1 to 4. This time the variables I included were age, whether the participant completed CR category, diagnosis category at referral, family history of coronary heart disease, diagnosis of diabetes, co-morbidity score, cholesterol level, deprivation score, baseline body mass index, [which I selected in lieu of the weight variable, as weight on its own without a height measurement is meaningless] and baseline perception level of social support.

I discarded each one that did not reach significance at 10%. However none of the variables with missing data were significant when added to the model. This left me with a model that contained the following variables: age; whether the participant completed CR category; diagnosis category at referral and co-morbidity score. Next, I added gender to the model, which although not significant previously [Table 11:9], became significant in the presence of the other variables. At the end of model fitting the best combination was a model [Table 11:11] that was exactly the same as the one created from the data set with complete data.

### **11.2.3 Building the model for cardiovascular mortality**

I generated the model for cardiovascular mortality in the same way by firstly using a data set with complete data [Table 11.10] and then repeating the process with the inclusion of the variables with missing data. The final model I selected [Table 11:11] contained the same variables as the model selection for deaths from all causes.

Finally, I systematically added the fitness and depression variables to the models that I had created as shown in Tables 11:12–11:21 to assess their impact on survival after adjusting for all other variables in the model.



Table 11:10 Deaths from cardiovascular causes. Hazard ratios reported using Cox proportional hazards regression for clinical and demographic variables

Variable	Participants	Deaths	Hazard Ratio	95% Confidence Interval	p value
Age, years	2714		1.068	1.053, 1.082	<0.001
Gender					
Male	2167	224 (10.3%)	1		0.797
Female	547	53 (9.69%)	0.961	0.712, 1.29	
Systolic blood pressure, mmHg	2699		1	0.995, 1.003	0.728
Diastolic blood pressure, mmHg	2688		0.995	0.980, 0.999	0.033
Referrals to CR					
Patients who completed CR	2054	165 (8.03%)	1		<0.001
Patients failing to complete CR	660	112 (17.0%)	2.39	1.88, 3.04	
Diagnostic category					
Myocardial infarction (MI)	1451	202 (13.9%)	1		<0.001
Coronary Artery Bypass Grafts	689	37 (5.37%)	0.412	0.290, 0.585	
PCI (Angioplasty)	251	9 (3.59%)	0.316	0.162, 0.617	
Angina Pectoris	169	17 (10.1%)	0.68	0.414, 1.12	
Other coronary heart disease pathology	54	9 (16.7%)	1.54	0.788, 3.005	
MI + PCI	100	3 (3.00%)	0.292	0.935, 0.917	

Variable	Participants	Deaths	Hazard Ratio	95% Confidence Interval	p value
No family history of coronary heart disease	1502	174 (11.6%)	1		
Family history of coronary heart disease	1212	103 (8.50%)	0.692	0.542, 0.883	0.003
Smoking history					0.655
Non-smoker (never)	813	78 (9.59%)	1		
Not for > 10 years	739	80 (10.8%)	1.21	0.844, 1.65	
Not for between 1-10 years	106	10 (9.43%)	1.17	0.607, 2.27	
Recent quitter < 1 year	818	81 (9.90%)	0.995	0.729, 1.36	
Current smoker	235	27 (11.5%)	1.22	0.786, 1.88	
No history of diabetes	2373	233 (9.82%)	1		
Reported previous history of diabetes	341	44 (12.9%)	1.59	1.15, 2.19	0.008
On full secondary prevention medication	528	27 (5.11%)	1		
Not on full secondary prevention medication	2186	250 (11.4%)	0.694	0.463, 1.039	0.064
Co-morbidity score					<0.001
None	1909	177 (9.27%)	1		
1 (least)	319	33 (10.3%)	1.16	0.801, 1.69	
2	397	47 (11.8%)	1.52	1.000, 2.10	
3	57	13 (22.8%)	3.35	1.903, 5.88	
4 (most)	32	7 (21.9%)	4.37	2.045, 9.34	



Variable	Participants	Deaths	Hazard Ratio	95% Confidence Interval	p value
<b>Occupational Code 1-9</b>					0.666
Managers & Senior officials	402	35(8.71%)	1		
Professional occupational	255	32 (12.5%)	1.56	0.964, 2.52	
Associate professional	251	22 (8.76%)	1.05	0.614, 1.78	
Administrative & secretarial	282	24 (8.51 %)	1.002	0.597, 1.69	
Skilled trade	582	61 (10.5)	1.25	0.824, 1.89	
Personal service	76	6 (7.89%)	1.030	0.433, 2.45	
Sales & customer	70	5 (7.14%)	0.863	0.338, 2.20	
Process, plant and machines	293	26 (8.87%)	1.05	0.629, 1.74	
Elementary occupations	210	23 (11.0%)	1.36	0.802, 2.30	
<b>Perception of level of social support</b>					0.549
Yes, as much as I wanted	1240	76 (6.13%)	1		
Yes, quite a bit	378	23 6.08%)	0.972	0.610, 1.55	
Yes, some	171	15 (8.77%)	1.45	0.833, 2.52	
Yes, a little	108	9 (8.33%)	1.43	0.713, 2.84	
No, not at all	42	4 (9.52%)	1.59	0.582, 4.35	
<b>Weight, kg</b>	2694		0.994	0.986, 1.002	0.158
<b>Body mass index, kg/m2</b>	1552		0.981	0.932, 1.0340	0.479
<b>Cholesterol mmol/L</b>	2177		1.18	1.051, 1.31	0.005
<b>Fasting triglycerides mmol/L</b>	1927		0.992	0.849, 1.16	0.928
<b>Index of Multiple Deprivation score</b>	2600		1.021	1.00, 1.041	0.046

**Table 11:11 Deaths from all causes and cardiovascular mortality.  
Hazard ratios for variables included in the final models**

	All-cause mortality Participants 2714 Deaths 451			Cardiovascular mortality Participants 2714 Deaths 277		
Variables	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.07	1.06, 1.08	<0.001	1.07	1.05, 1.08	<0.001
Gender			0.013			0.012
Male	1.00			1.00		
Female	0.75	0.59, 0.94		0.73	0.54, 0.99	
Referrals to CR			<0.001			<0.001
Completed CR	1.00			1.00		
Did not complete CR	2.28	1.88, 2.76		2.24	1.75, 2.86	
Diagnostic category			<0.001			<0.001
MI	1.00			1.00		
CABG	0.54	0.42, 0.70		0.43	0.31, 0.62	
PCI	0.39	0.23, 0.66		0.38	0.19, 0.74	
Angina Pectoris	0.70	0.47, 1.03		0.67	0.41, 1.09	
Other CHD	1.22	0.70, 2.13		1.31	0.67, 2.56	
MI + PCI	0.42	0.17, 1.02		0.39	0.12, 1.23	
Co-morbidity score			<0.001			0.004
None	1.00			1.00		
1 (least)	1.22	0.93, 1.61		0.97	0.67, 1.41	
2	1.58	1.23, 2.02		1.33	0.96, 1.84	
3	2.63	1.68, 4.12		2.41	1.36, 4.25	
4 (most)	3.95	2.24, 6.97		3.21	1.49, 6.93	

The impact of the hazard ratio for age in all the models was constant.



**Table 11:12 Deaths from all causes and cardiovascular mortality.  
Hazard ratios with the inclusion of baseline fitness**

	All-cause mortality Participants 2714 Deaths 451			Cardiovascular mortality Participants 2714 Deaths 277		
Variables	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.05	1.04, 1.07		1.04	1.03, 1.06	
Gender						
Male	1.00			1.00		
Female	0.61	0.48, 0.78		0.53	0.39, 0.74	
Referrals to CR						
Completed CR	1.00			1.00		
Did not complete CR	2.06	1.70, 2.51		1.92	1.50, 2.47	
Diagnostic category						
MI	1.00			1.00		
CABG	0.54	0.42, 0.70		0.44	0.31, 0.62	
PCI	0.46	0.27, 0.79		0.49	0.25, 0.96	
Angina Pectoris	0.71	0.48, 1.05		0.69	0.42, 1.31	
Other CHD	1.28	0.73, 2.24		1.38	0.71, 2.71	
MI + PCI	0.45	0.18, 1.09		0.44	0.14, 1.38	
Co-morbidity score						
None	1.00			1.00		
1 (least)	1.14	0.86, 1.50		0.87	0.59, 1.27	
2	1.43	1.12, 1.84		1.14	0.83, 1.59	
3	2.07	1.32, 3.27		1.69	0.95, 3.00	
4 (most)	3.38	1.91, 5.98		2.54	1.17, 5.51	
Baseline Fitness level			<0.001			<0.001
High	1.00			1.00		
Medium	1.93	1.41, 2.63	<0.001	2.95	1.87, 4.64	<0.001
Low	2.83	2.02, 3.96	<0.001	5.40	3.36, 8.69	<0.001

The effect of baseline fitness level on mortality was significant.

**Table 11:13 Deaths from all causes and cardiovascular mortality.  
Hazard ratios with inclusion of baseline depression**

	All-cause mortality Participants 2625 Deaths 424			Cardiovascular mortality Participants 2625 Deaths 257		
Variables	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.07	1.06, 1.08		1.07	1.07, 1.09	
Gender						
Male	1.00			1.00		
Female	0.71	0.56, 0.91		0.68	0.49, 0.93	
Referrals to CR						
Completed CR	1.00			1.00		
Did not complete CR	2.28	1.86, 2.78		2.21	1.71, 2.86	
Diagnostic category						
MI	1.00			1.00		
CABG	0.53	0.41, 0.69		0.42	0.29, 0.60	
PCI	0.39	0.22, 0.68		0.37	0.18, 0.75	
Angina Pectoris	0.68	0.45, 1.02		0.62	0.37, 1.06	
Other CHD	1.12	0.58, 2.19		1.16	0.51, 2.62	
MI + PCI	0.43	0.18, 1.05		0.41	0.13, 1.29	
Co-morbidity score						
None	1.00			1.00		
1 (least)	1.18	0.89, 1.57		0.90	0.61, 1.33	
2	1.55	1.20, 2.01		1.33	0.96, 1.86	
3	2.46	1.53, 3.95		2.12	1.14, 3.93	
4 (most)	4.17	2.34, 7.43		3.38	1.55, 7.38	
Baseline Depression score			0.076			0.071
0-<8 (none)	1.00			1.00		
8-10	0.98	0.72, 1.34	0.893	0.92	0.61, 1.39	0.695
11-21 (suggests clinical depression)	1.60	1.09, 2.35	0.017	1.79	1.11, 2.87	0.017

There is evidence that a depression score greater than 10 increases mortality for both all-cause deaths and cardiovascular deaths.



**Table 11:14 Deaths from all causes and cardiovascular mortality.  
Hazard ratios with inclusion of baseline fitness & baseline depression**

	All-cause mortality Participants 2625 Deaths 424			Cardiovascular mortality Participants 2625 Deaths 257		
Variables	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.06	1.04, 1.07		1.05	1.03, 1.06	
Gender						
Male	1.00			1.00		
Female	0.60	0.46, 0.77		0.51	0.37, 0.71	
Referrals to CR						
Completed CR	1.00			1.00		
Did not complete CR	2.06	1.68, 2.53		1.89	1.46, 2.46	
Diagnostic category						
MI	1.00			1.00		
CABG	0.53	0.41, 0.70		0.42	0.29, 0.61	
PCI	0.45	0.26, 0.80		0.46	0.22, 0.94	
Angina Pectoris	0.69	0.46, 1.04		0.64	0.38, 1.09	
Other CHD	1.11	0.57, 2.17		1.13	0.50, 2.56	
MI + PCI	0.44	0.18, 1.09		0.43	0.14, 1.37	
Co-morbidity score						
None	1.00			1.00		
1 (least)	1.11	0.83, 1.47		0.81	0.55, 1.20	
2	1.44	1.11, 1.86		1.18	0.85, 1.65	
3	1.99	1.23, 3.22		1.54	0.83, 2.88	
4 (most)	3.73	2.09, 6.65		2.86	1.31, 6.27	
Baseline Fitness level			<0.001			<0.001
High	1.00			1.00		
Medium	1.82	1.32, 2.49	<0.001	2.63	1.66, 4.16	<0.001
Low	2.66	1.89, 3.75	<0.001	4.90	3.03, 7.95	<0.001
Baseline Depression score						
0-<8 (none)	1.00			1.00		
8-10	0.93	0.68, 1.27	0.633	0.84	0.55, 1.27	0.405
11-21 (suggests clinical depression)	1.45	0.98, 2.13	0.061	1.52	0.94, 2.45	0.086

The effect of baseline depression was attenuated when added to the model.

**Table 11:15 Deaths from all causes and cardiovascular mortality.  
Hazard ratios with the inclusion of fitness level after cardiac  
rehabilitation**

	All-cause mortality Participants 1398 Deaths 180			Cardiovascular mortality Participants 1398 Deaths 106		
Variables	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.05	1.03, 1.07		1.03	1.01, 1.06	
Gender						
Male	1.00			1.00		
Female	0.61	0.41, 0.92		0.47	0.27, 0.82	
Diagnostic category						
MI	1.00			1.00		
CABG	0.43	0.29, 0.64		0.29	0.16, 0.54	
PCI	0.25	0.08, 0.80		0.28	0.07, 1.15	
Angina Pectoris	0.83	0.46, 1.51		0.75	0.35, 1.64	
Other CHD	2.10	0.92, 4.79		2.62	1.05, 6.53	
MI + PCI	0.61	0.20, 1.85		1.32	0.38, 4.57	
Co-morbidity score						
None	1.00			1.00		
1 (least)	1.23	0.80, 1.88		0.86	0.47, 1.59	
2	1.28	0.82, 2.00		0.97	0.52, 1.80	
3	1.95	0.84, 4.51		1.45	0.45, 4.70	
4 (most)	6.46	2.53, 16.5		1.03	0.12, 8.56	
Fitness level after CR			<0.001			<0.001
High	1.00			1.00		
Medium	2.47	1.70, 3.58	<0.001	3.68	2.23, 6.07	<0.001
Low	4.23	2.64, 6.79	<0.001	6.37	3.37, 12.0	<0.001

The effect of adding fitness level after CR was also strongly significant.



**Table 11:16 Deaths from all causes and cardiovascular mortality.  
Assessing the effect of fitness levels before cardiac rehabilitation after  
adjusting for fitness levels after cardiac rehabilitation**

	All-cause mortality Participants 1398 Deaths 180			Cardiovascular mortality Participants 1398 Deaths 106		
Variables	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.04	1.02, 1.06		1.03	1.00, 1.05	
Gender						
Male	1.00			1.00		
Female	0.58	0.39, 0.87		0.43	0.25, 0.75	
Diagnostic category						
MI	1.00			1.00		
CABG	0.42	0.28, 0.63		0.29	0.16, 0.53	
PCI	0.27	0.08, 0.85		0.30	0.07, 1.23	
Angina Pectoris	0.83	0.46, 1.52		0.76	0.35, 1.66	
Other CHD	2.18	0.95, 5.00		2.78	1.11, 6.94	
MI + PCI	0.66	0.22, 2.03		1.50	0.43, 5.21	
Co-morbidity score						
None	1.00			1.00		
1 (least)	1.20	0.78, 1.85		0.84	0.46, 1.55	
2	1.24	0.79, 1.94		0.91	0.49, 1.69	
3	1.80	0.77, 4.16		1.27	0.39, 4.11	
4 (most)	5.74	2.24, 14.7		0.88	0.11, 7.23	
Fitness level after CR						
High	1.00					
Medium	1.72	1.11, 2.67	0.016	2.06	1.14, 3.73	0.017
Low	2.53	1.38, 4.65	0.003	2.66	1.21, 5.87	0.015
Fitness level before CR			<0.001			<0.001
High	1.00					
Medium	1.86	1.06, 3.25	0.030	2.37	1.07, 5.27	0.034
Low	2.53	1.27, 5.02	0.008	4.29	1.70, 10.8	0.002

Whilst there is an effect of fitness after CR on survival, even after adjusting for this, there is an effect of fitness before CR.

**Table 11:17 Deaths from all causes and cardiovascular mortality.  
Hazard ratios with the inclusion of depression score after cardiac  
rehabilitation**

	All-cause mortality Participants 1965 Deaths 259			Cardiovascular mortality Participants 1965 Deaths 156		
Variables	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.07	1.05, 1.08		1.06	1.04, 1.08	
Gender						
Male	1.00			1.00		
Female	0.78	0.57, 1.08		0.78	0.52, 1.18	
Diagnostic category						
MI	1.00			1.00		
CABG	0.41	0.29, 0.57		0.30	0.18, 0.49	
PCI	0.18	0.07, 0.49		0.14	0.03, 0.57	
Angina Pectoris	0.79	0.47, 1.32		0.77	0.40, 1.47	
Other CHD	0.93	0.38, 2.27		1.18	0.43, 3.24	
MI + PCI	0.40	0.14, 1.12		0.54	0.16, 1.77	
Co-morbidity score						
None	1.00			1.00		
1 (least)	1.22	0.84, 1.76		0.85	0.50, 1.43	
2	1.30	0.92, 1.85		1.01	0.62, 1.63	
3	2.80	1.37, 5.72		2.02	0.74, 5.53	
4 (most)	8.88	3.72, 21.2		4.31	0.10, 18.6	
Depression level after CR			0.454			0.116
0-<8 (none)	1.00			1.00		
8-10	1.33	0.72, 2.44	0.893	1.83	0.93, 3.60	0.080
11-21 (suggests clinical depression)	0.87	0.21, 3.54	0.017	0.69	0.10, 4.99	0.713

There was no evidence that depression level after CR had an effect on survival.



**Table 11:18 Deaths from all causes and cardiovascular mortality.  
Hazard ratios for change in fitness levels between baseline and after  
cardiac rehabilitation**

	All-cause mortality Participants 1398 Deaths 180			Cardiovascular mortality Participants 1398 Deaths 106		
Variables	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.07	1.05, 1.09		1.07	1.04, 1.09	
Gender						
Male	1.00			1.00		
Female	0.89	0.61, 1.31		0.75	0.44,1.28	
Diagnostic category						
MI	1.00			1.00		
CABG	0.41	0.27, 0.61		0.27	0.15, 0.50	
PCI	0.20	0.06, 0.64		0.21	0.05, 0.87	
Angina Pectoris	0.89	0.49, 1.61		0.81	0.37, 1.78	
Other CHD	2.23	0.97, 5.12		.95	1.18, 7.41	
MI + PCI	0.66	0.23, 1.90		1.09	0.33, 3.63	
Co-morbidity score						
None	1.00			1.00		
1 (least)	1.19	0.78, 1.83		0.82	0.44, 1.51	
2	1.35	0.87, 2.11		1.04	0.56, 1.93	
3	2.87	1.25, 6.59		2.24	0.70, 7.18	
4 (most)	6.69	1.74, 16.4		1.38	0.18, 10.7	
Change in fitness in ml/kg/min	0.97	0.92, 1.02	0.220	0.96	0.90, 1.03	0.285

Table 11:18 shows the hazard ratios for the incremental change in fitness [VO<sub>2peak</sub>] between the start and end of the CR programme when this variable is added to the model. This indicated that an additional increase in fitness of 1ml/kg/min is associated with a reduction in risk of 3% for all-cause mortality and 4% in cardiovascular mortality, although this was not significant (p=0.220 and p= 0.285 respectively).

**Table 11:19 Deaths from all causes and cardiovascular mortality.  
Hazard ratios for change in depression score between baseline and  
after cardiac rehabilitation**

	All-cause mortality Participants 1939 Deaths 252			Cardiovascular mortality Participants 1939 Deaths 152		
Variables	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.07	1.05, 1.08		1.06	1.04, 1.08	
Gender						
Male	1.00			1.00		
Female	0.81	0.58, 1.12		0.82	0.54, 1.24	
Diagnostic category						
MI	1.00			1.00		
CABG	0.40	0.28, 0.57		0.30	0.18, 0.50	
PCI	0.19	0.07, 0.50		0.14	0.04, 0.59	
Angina Pectoris	0.78	0.46, 1.33		0.74	0.37, 1.46	
Other CHD	1.17	0.48, 2.87		1.46	0.54, 4.00	
MI + PCI	0.42	0.15, 1.20		0.58	0.17, 1.91	
Co-morbidity score						
None	1.00			1.00		
1 (least)	1.25	0.87, 1.81		0.88	0.52, 1.49	
2	1.32	0.92, 1.88		1.04	0.64, 1.69	
3	2.78	1.36, 5.69		2.00	0.73, 5.45	
4 (most)	8.73	3.66, 20.8		4.22	0.98, 18.2	
Change in depression, in single units	1.03	0.98, 1.09	0.188	1.03	0.97, 1.10	0.318

When change in depression scores between baseline and exit assessments was added to the model this showed that the risk of both all-cause and cardiovascular mortality increased by 3% per unit increase on the HADS, although this was not found to be significant for either all cause (p=0.188) or for cardiovascular deaths (p= 0.318).



Improvement in fitness is intuitively more valuable to people who start from a low fitness base rather than for people who are already fit at the start of a physical training programme. I therefore decided to repeat the analysis in Table 11:18 to obtain 3 estimates of the change in fitness by the 3 levels of fitness category, high, medium and low for all-cause and cardiovascular mortality. The results from this analysis are shown in Tables 11:20 and 11.21. The effect of change in fitness on mortality varied with the baseline fitness level. For those whose baseline fitness levels fell in the high or medium categories, change in fitness did not affect either all-cause or cardiovascular mortality. However for those who were least fit, with a low fitness level at baseline, increasing fitness was associated with a significant reduction in mortality, with an effect of an 11% reduction in both all-cause and cardiovascular mortality for each increase in fitness of 1ml/kg/min.

Table 11:20 All-cause mortality. Hazard ratios for change in fitness levels by fitness category

Variables	All-cause mortality High Fitness Category Participants 535 Deaths 21			All-cause mortality Medium Fitness Category Participants 539 Deaths 79			All-cause mortality Low Fitness Category Participants 324 Deaths 80		
	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.12	1.07, 1.20		1.04	1.01, 1.07		1.03	1.00, 1.05	
Gender									
Male	1.00			1.00			1.00		
Female	0.90	0		0.69	0.34, 1.40		0.50	0.30, 0.83	
Diagnostic category									
MI	1.00			1.00			1.00		
CABG	0.12	0.15, 0.90		0.45	0.25, 0.81		0.44	0.24, 0.79	
PCI	1.11	0.30, 4.05		1.75e-15	0		7.10e-19	0	
Angina Pectoris	1.87	0.40, 8.71		1.05	0.45, 2.45		0.45	0.16, 1.26	
Other CHD	4.10	0.48, 35.4		1.16	0.16, 8.55		2.96	1.04, 8.40	
MI + PCI	1.21	0.15, 9.52		0.38	0.41, 3.48		0.86	0.18, 4.16	
Co-morbidity score									
None	1.00			1.00			1.00		
1 (least)	0.58	0.13, 2.67		1.25	0.65, 2.42		1.54	0.81, 2.92	
2	7.35e-18	0		1.07	0.50, 2.27		1.74	0.97, 3.14	
3	8.04 e-18	0		9.25	3.18, 26.9		0.79	0.19, 3.28	
4 (most)	2.32 e-18	0		10.08	2.64, 38.4		3.19	0.83, 12.3	
Change in fitness in ml/kg/min	1.08	0.92, 1.27	0.350	0.96	0.88, 1.05	0.426	0.89	0.82, 0.96	0.005



Table 11:21 Cardiovascular mortality. Hazard ratios for change in fitness levels by fitness category

Variables	Cardiovascular mortality High Fitness Category Participants 535 Deaths 10			Cardiovascular mortality Medium Fitness Category Participants 539 Deaths 44			Cardiovascular mortality Low Fitness Category Participants 324 Deaths 52		
	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Age, in 1 year increase	1.15	1.06, 1.23		1.03	0.99, 1.07		1.01	0.98, 1.04	
Gender									
Male	1.00			1.00			1.00		
Female	0	0		0.26	0.62, 1.09		0.48	0.26, 0.89	
Diagnostic category									
MI	1.00			1.00			1.00		
CABG	0	0		0.26	0.10, 0.67		0.35	0.15, 0.79	
PCI	1.59	0.31, 8.23		0	0		0	0	
Angina Pectoris	2.97	0.33, 27.1		1.05	0.37, 3.00		0.35	0.84, 1.48	
Other CHD	13.0	1.38, 123.0		1.56	0.21, 11.8		3.80	1.12, 12.8	
MI + PCI	2.24	0.26, 19.4		0	0		2.12	0.42, 10.7	
Co-morbidity score									
None	1.00			1.00			1.00		
1 (least)	0	0		1.27	0.56, 2.89		0.82	0.31, 2.13	
2	0	0		0.70	0.21, 2.31		1.21	0.57, 2.56	
3	0	0		3.67	0.48, 28.1		1.05	0.25, 4.40	
4 (most)	0	0		0	0		0.98	0.10, 9.49	
Change in fitness in ml/kg/min	1.12	0.90, 1.38	0.309	0.93	0.83, 1.05	0.250	0.89	0.80, 0.98	0.019

## Reference: Chapter 11

Collett D (1994): *Modelling survival data in medical research. Texts in Statistics Science*. London: Chapman & Hall.



# Chapter 12

## Discussion

### ***12.1 Overview of this study***

This study reports the long term outcomes for an unselected group of 2,714 patients with coronary heart disease who enrolled in a CR programme. Measures of physical fitness and depression were compared with prognosis. The participants were followed up for nearly 13 years, providing more than 18,000 person years of observation.

Between the start and finish of our Phase III programme the mean increase in fitness for the cohort was 16.8%. Thirty-three percent of participants showed an improvement in their fitness category and less than 1% showed a deterioration. The prevalence of symptoms suggestive of clinical depression at baseline was less than 5% and this had reduced to 1.13% by the follow-up assessment. Fitness levels were significantly related to depression scores; the participants who were least fit were more likely to be depressed.

At the end of the study period 16.6% of the cohort had died. Almost two-thirds of the deaths were from cardiovascular causes. The study confirms that fitness levels are related to mortality in patients with coronary heart disease who have been enrolled in a CR programme.

An important finding from this study was that an increase in fitness amongst those who were least fit at baseline was associated with an 11% reduction in the risk of cardiovascular mortality for each unit increase in fitness of one ml/kg/min. This study, therefore, has shown a significant protective effect of improvement in fitness for those in the lowest fitness category at baseline, although there was no evidence of survival benefit from improvement in fitness in those participants who were in the medium or high fitness categories at baseline.

Results from this study also showed an association at the start of Phase III CR between symptoms suggestive of clinical depression [HADS depression score <10] and mortality before adjusting for fitness, although there was no association evident between depression assessed at the end of the programme and mortality.

As far as I can determine, this study is the only long term observational study which has looked at the combined effects of physical fitness and depression on mortality in patients with coronary heart disease. It is also the largest study to examine the relationship between fitness and mortality, and depression and mortality in exercising coronary patients who are enrolled in a CR programme.



## ***12.2 Strengths of this study***

One of the main strengths of my study is that the participants were not selected in any way, but were typical of people with coronary disease enrolling in a CR programme in southern England. This gives the study high external validity or generalisability (Black 1996).

With 18,000 person years of follow up, this study was seven times larger than the only equivalent observational study of fitness and mortality in CR participants (Vanhees et al 1995) and four times larger than the largest observational study of depression and mortality in coronary heart disease patients (Blumenthal et al 2004).

The demographic and epidemiological data have been collected consistently and systematically. Throughout the study period I oversaw the organisation and administration of the CR programme, which included all data collection. All the study participants received a similar style and standard of individualised intervention for the duration of the study period.

The long term mortality data on our patients was, as far as I can ascertain, complete and reliable, as it was based on the mortality data obtained from the Office for National Statistics.

The majority of the patients referred to Phase III CR are probably stratified as low risk and the higher risk patients who have the most to gain are often

excluded. Most of the observational studies and randomised controlled trials only included participants who were at low risk of succumbing to a further cardiovascular event, (Bethell and Mullee 1990; Dugmore et al 1999; Fioretti et al 1988; Hofman-Bang et al 1999; Jolliffe et al 2003; Marra et al 1985; PRECOR 1991; Taylor et al 2004; Vanhees et al 1995; Vanhees et al 1994; Vermeulen et al 1983). This may be because it is perceived as too dangerous or too time consuming to include high risk patients in Phase III exercise sessions. A further strength in this study is the inclusion of patients stratified as high risk, for example those awaiting bypass surgery and those with ischaemic heart failure.

Finally, we recorded information on co-morbidity during the patient's initial clinical assessment. I found only two studies that had accounted for the shorter term effects of non-cardiovascular co-morbidity on mortality (Blumenthal et al 2004; Grace et al 2005) which I discussed in Chapter 7 page 171 and Chapter 5 page 126, and none which accounted for the longer term effect of co-morbidity on outcomes. One reason for this is that early research tended to concentrate on a younger male coronary population for whom co-morbid illness was relatively uncommon. In this study I built on the original research to create an index of co-morbidities specific to CR carried out by Zoghbi et al (Zoghbi et al 2004) which I included in my analyses, and which proved to be an important aspect of my research. Co-morbidity was found to be a significant confounder in prediction of mortality.



### ***12.3 Limitations of the study***

The study was limited by 4 main factors. Firstly, the methods we used to measure fitness. Secondly, the instruments we used to assess depression. Thirdly, the patients we excluded from the analyses and fourthly the stringent definition of adequate secondary prevention medication.

#### **12.3.1 Measuring fitness**

Measuring fitness is difficult in a community venue such as ours, as a Sports Centre gymnasium is very different from a controlled laboratory environment.

We used two methods to measure cardiorespiratory fitness levels: cycle ergometry and treadmill testing. For the first part of the study we used a cycle ergometer because we did not have access to a treadmill until August 1995. In August 1995 we obtained a treadmill and thereafter used this routinely to assess patients. However, we continued to use cycle ergometry for the very few patients who were unable to walk on a treadmill, usually because of orthopaedic limitations.

Exercise testing carried out on a treadmill has an advantage over cycle ergometry in that this method measures cardiovascular changes induced by a commonly performed exercise – i.e. walking, whereas tests performed on cycle ergometers are not usually pertinent to daily activities. For each patient we always used the same method for exercise testing at the start and finish of the programme.

We predicted oxygen uptake [ $\text{VO}_{2\text{peak}}$ ] from the known oxygen costs of bicycling at different workloads or the oxygen uptake per kilogram of body weight for different levels of treadmill exercise, as described in Chapter 9 page 243. Predicted oxygen uptake for both bicycle and treadmill exercise differs from measured oxygen uptake. When compared with expired gas analysis, cycling overestimates oxygen uptake by about 10% (Shephard 1979). On the other hand, treadmill exercise underestimates oxygen uptake by approximately 5% (Shephard et al 1968). Therefore the participants from the earlier years of the study who were tested by cycle ergometry were slightly more likely to be included in higher fitness groups. We have no way of correcting this small bias. In addition, the changes in physical fitness between baseline and follow up, even though they were always measured by the same technique, would likewise be subject to a small bias.

For all but nine months of the study period the same doctor supervised all the exercise tests. It is possible that the manner in which a different doctor performed the tests in the last nine months differed slightly, although we made every effort to ensure that the approach adopted by the two doctors was consistent.

### **12.3.2 Measuring depression**

We used the HADS depression subscale to measure depression with a threshold of 7 for no depression, 8 to 10 for borderline symptoms and a score of greater than 10 for symptoms suggestive of clinical depression.



The baseline level of depression in this study was lower than in other studies using different instruments. The choice of instrument used to detect depressive symptoms or depressive disorders may have affected the results I obtained. We did not have sufficient resources to use structured interviews, considered to be a superior way to assess psychological health.

A further limitation in my study was the small size of the clinically depressed group of patients [67 participants]. I did not have sufficient power therefore to show any effect on changes in depression scores between the start and end of CR as there were only 29 deaths reported in the clinically depressed

### **12.3.3 Participants excluded from analysis**

The cohort for this study consisted of participants for whom we had collected fitness data. It was clear from my primary analysis, which compared participants with fitness data and those without, that the fitness data group was significantly different [Table 10:1 page 261] from the group without fitness data. The participants without fitness data were older, more likely to be female, to have enrolled into CR with a myocardial infarction than after revascularisation procedures and have greater co-morbid disease ( $p < 0.001$ ).

### **12.3.4 The definition of full secondary prevention medication**

In this study I used a very stringent definition of the term 'adequate' secondary prevention. I had created a new variable called 'On Full Secondary Prevention' to log whether the patients were taking full secondary

prevention medication or not, i.e. by combining the 4 standard secondary prevention medications: aspirin, a  $\beta$  blocker, an ace inhibitor and a statin into a single dichotomous variable. Since statins were not widely available until the mid 90s for the patients in this study, and also ace inhibitors were similarly less commonly prescribed until midway through the study period this is a further limitation of this study.

**12.4 Comparison with previous studies comparing measures of fitness and depression with long term mortality**

**12.4.1 Age and gender**

The mean age of participants in my study was 62 years. Table 12:1 shows age and gender comparisons between this study and previous research that I reviewed in Chapter 4 page 61. The mean age of participants in this study was greater than reported in comparable study cohorts. Our patients were unselected CR attendees, for whom enrolment had not been limited by either age or gender.

**Table 12:1 Comparisons of age and gender**

Authors, year, country of origin	Mean age, years [ $\pm$ sd]		
	Males	Females	% Female
Vanhees et al 1994, Belgium	53 [ $\pm$ 8]	0	0
Vanhees et al 1995, Belgium	53 [ $\pm$ 8]	0	0
Kavanagh et al 2002 ,Canada	55 [ $\pm$ 9]	0	0
Kavanagh et al 2003,Canada		59 [ $\pm$ 10]	100
Awad-Elkarim et al 2003,UK	48	0	18
This study	61 [ $\pm$ 10]	65[ $\pm$ 9]	20



### **12.4.2 Smoking habit**

We had recorded data on smoking habit for 99.9% of participants who were assessed at the start of Phase III. Nine percent of participants were current smokers and 30% had never smoked [Table 10:4 page 270]. This compares with Vanhees' research where 6% of participants were still smoking at baseline assessment (Vanhees 1995) and 17% who had no previous history of smoking. In Kavanagh's study 16.2% of males (Kavanagh et al 2002) and 12.5% of females were current smokers and 39% of females had never smoked (Kavanagh et al 2003). Kavanagh did not report past smoking history for his male cohort.

The differences in proportion of current smokers in the various studies may reflect the background fall in smoking prevalence in North America, parts of Europe and the United Kingdom. Kavanagh's studies straddled the late 60s, 70s and late 80s, Vanhees' study the late 70s and 80s, whereas this study was carried out mainly in the nineties through to just beyond the millennium.

### **12.4.3 Co-morbidity**

I found that 3.2% of participants reported moderately severe non-cardiac and non-psychiatric co-morbid disease and a further 1.2% had severe disease [Table 10:4 page 270]. Thirty percent of participants had no co-morbidity. Grace et al's study which I discussed in Chapter 5 page 126 [Table 5:2] also reported that a similar proportion [29%] of acute coronary syndrome survivors from their cohort had no co-morbidity at baseline (Grace et al 2005).

Little is known about the prevalence of co-morbid illness in the coronary population, and particularly those who have attended CR programmes. Moreover, the importance of the prognostic effect of non-cardiac co-existing illness on outcomes in coronary heart disease patients has rarely been considered. Most researchers have accounted only for co-morbidity that could have a large effect on survival such as diabetes, heart failure or end stage renal disease with the exception of the ENRICHD researchers (Berkman et al 2003; Blumenthal et al 2004; Blumenthal et al 1997) who used the D'Hoore Co-morbidity Index (D'Hoore et al 1996) to measure co-morbidity in their large multicentre clinical trial [Chapter 7 page 171]. There are two possible explanations for this. Firstly, patients enrolled in most studies have been younger and therefore less likely to have concomitant co-morbidity and secondly those with important co-morbidity often fail to be referred or enrolled into CR in the first place.

#### **12.4.4 Fitness**

The median estimated baseline fitness as measured by  $VO_{2peak}$  for males in this study was 20.2 ml/kg/min., identical to that found by Kavanagh in his cohort of younger patients who would therefore be expected to be fitter than ours (Kavanagh et al 2002). There are two reasons that may explain why his patients were less fit than might be expected. Firstly, in Kavanagh's study  $VO_{2peak}$  was measured by expired gas analysis in laboratory type conditions, rather than estimated as we had done. As already mentioned in section



12:3.1 of this chapter it is difficult to directly compare the different methods of exercise testing in these instances. Secondly, his patients were tested at 9-18 weeks post event compared to our 4-6 weeks. This would give them a longer period of physical detraining prior to starting CR. It may be that our patients were recruited to CR in an era when patients were mobilised more rapidly and therefore when they commenced the Phase III programme were fitter compared with Kavanagh's patients, who waited up to 18 weeks to begin their supervised exercise.

The mean  $VO_{2peak}$  of Vanhees' patients, also measured directly rather than estimated (Vanhees 1995), was 23.7 ml/kg/min and this level of fitness was greater than our patients, as would be expected from their younger mean age.

The median baseline fitness for females in this study measured by  $VO_{2peak}$  was 14.0 ml/kg/min as compared with Kavanagh's figure of 15.1 ml/kg/min in a rather younger sample. The mean age of our female participants was 65 years whereas the mean age of Kavanagh's patients was 59 years [Table 12:2].

Our participants' cardiorespiratory fitness had increased by 16.8% ( $p < 0.001$ ) at the second assessment at the end of CR [Table 10:5 page 275]. Vanhees reported an increase in cardiorespiratory fitness of 33% in his younger male cohort (Vanhees 1995). One reason for the greater increase in fitness seen

in Vanhees' patients may be that they had more supervised training hours per week. Our patients usually attended twice weekly exercise classes of one hour's duration, whereas Vanhees' patients had received 4 hours of supervised physical training each week.

#### **12.4.5 Depression**

The prevalence of depression in the general population in the United Kingdom is 5% (Ohayon et al 1999) which is remarkably similar to the baseline level in my cohort. However, in my study the prevalence of clinical depression at baseline [n=122/2625] (4.6%) and outcome (~1%) was low when compared to levels reported from most other studies of depression and coronary heart disease, which I discussed in Chapter 5. There are several possible reasons for this. Comparisons between the prevalence of depression in this study and other similar study cohorts are shown in Table 12:2. At baseline only 4.6% of our participants had symptoms suggestive of clinical depression [scoring > 10 on the HADS] and 10.6% were in the borderline category [with scores between 8 and 10]. Combining the percentages for symptoms suggestive of clinical depression with borderline cases gave an overall result of 15.2%. By contrast, van Melle's meta-analysis of studies on myocardial infarction survivors, depression and cardiovascular prognosis [Chapter 5 page 117] showed a baseline prevalence to range from 5 to 47% in the 37 studies he had included (van Melle et al 2004). The only other comparable study from the United Kingdom that had used the HADS, and had also used the same cut-off points as I



have, reported a 7.6% prevalence of in-hospital depression post infarction with 9.9% of patients reporting borderline symptoms. This gave an overall combination of depression and borderline symptoms of 17.5% (Mayou et al 2000). Our patients completed baseline psychological assessment at the start of Phase III which was about 4-6 weeks later on than Mayou's patients.

**Table 12:2    Prevalence of baseline depression in selected study cohorts**

Authors, year, country of origin	% Baseline Depression	
	Depressive symptoms	Depressive disorders
Carney, 1988, USA		17%
Ahern, 1990, USA	40%	
Ladwig, 1994, Germany		15%
Frasure-Smith 1995, 2000, Canada	32%	16%
Denollet, 1996, The Netherlands	41.9%	
Barefoot 1996, USA	11.1%	
Mayou 2000, UK	7.6%	
	+ borderline symptoms 9.9%	
Penninx 2001, The Netherlands	19.7%	
Connerney 2001, USA		20.3%
Lane 2002, UK	30%	
Blumenthal 2003, USA	38%	
Grace 2005, Canada	31.3%	
This study	4.6%	
	+ borderline symptoms 10.6%	

This may help to explain the slightly lower prevalence of depression in my study.

Several researchers have acknowledged that there is no consistency in the instruments used to assess depression (Barth et al 2004; Frasure-Smith and Lesperance 2005). Some studies used interview techniques whilst others use questionnaires or a mix of both. Table 12:3 shows the different instruments used to assess depression in a selection of these studies. Results from the studies that used the BDI showed a consistently higher prevalence of depression, ranging from 30%-40% when the questionnaire was administered within 6-60 days following myocardial infarction (Ahern et al 1990; Frasure-Smith et al 2000; Frasure-Smith et al 1995; Grace et al 2005; Lane et al 2002).



**Table 12:3 Depression measures in selected study cohorts**

Authors, year, country of origin	Depression measure	% Baseline depressive symptoms	% Baseline depressive disorders
Carney 1988 , USA	Interview		17%
Ahern, 1990, USA	BDI	40%	
Ladwig, 1994, Germany	Interview		15%
Frasure-Smith 1995, 2000, Canada	BDI and Interview	32%	16%
Denollet, 1996, The Netherlands	Type D	41.9%	
Barefoot 1996, USA	Zung	11.1%	
Mayou 2000, UK	HADS	7.6%	
Penninx 2001, The Netherlands	CESD	19.7%	
Connerney 2001, USA	Interview		20.3%
Lane 2002, UK	BDI	30%	
Blumenthal 2003, USA	CESD	38%	
Grace 2005, Canada	BDI	31.3%	
This study	HADS	4.6%	

The timing of the psychological assessment in relation to a cardiac event or procedure may be an important consideration when comparing the prevalence rates of depression across different studies. Van Melle's meta-analysis showed that there was no uniformity in the timings of psychological assessments in the 37 studies he had included (van Melle 2004). For example, one study had assessed depression on Day 1 and Day 63 (Silverstone 1987) whilst approximately a third had measured depression within the first week after infarction. Some assessments occurred during hospitalisation and others in out patient clinics or during angiography. Frasure-Smith also reported similar findings from her more recent systematic

review of the literature relating depression and depressive symptoms with outcomes in people with coronary heart disease (Frasure-Smith and Lesperance 2005). Comparisons between the timings of assessments, venues and prevalence of depression are shown in Table 12:4

**Table 12:4 Timing, place of assessments and prevalence of depression in selected study cohorts**

Authors, year, country of origin	Timing and/or place of assessment	% Baseline depressive symptoms	% Baseline depressive disorder
Carney 1988 , USA	Out-patient angiography		17%
Ahern, 1990, USA	6-60 days post MI	40%	
Ladwig, 1994, Germany	3 weeks post MI		15%
Frasure-Smith 1995, 2000, Canada	In hospital post MI	32%	16%
Denollet, 1996, The Netherlands	Out-patient angiography	41.9%	
Barefoot 1996, USA	Out-patient CHD	11.1%	
Mayou 2000, UK	In hospital post MI	7.6%	
Penninx 2001, The Netherlands	Out-patient CHD	19.7%	
Connerney 2001, USA	In hospital post CABG		20.3%
Lane 2002, UK	In hospital post MI	30%	
Blumenthal 2003, USA	Day before CABG	38%	
Grace 2005, Canada	In hospital post acute coronary syndrome	31.3%	
This study	28 – 42 days post MI, post revascularisation, or with CHD	4.6%	

In the United Kingdom in particular, little is known about the level of depression scores for coronary heart disease patients during Phase III CR (Rees et al 2004). Since 1997 The British Association for Cardiac Rehabilitation with the British Heart Foundation have circulated all the CR programmes within the United Kingdom with an annual questionnaire. This



questionnaire asks for numbers and diagnoses of the patients treated in the CR programmes and outcome data for the patients (Bethell et al 2004). All CR programmes in the United Kingdom are encouraged to use the HADS to measure psychological state. The annual survey for the year 2001, which reflects data collection from the previous year, asked CR co-ordinators about the numbers of patients with HADS depression scores of 8 or more i.e. combining the symptoms suggestive of borderline and the clinical depression categories. This is the only occasion on which the survey requested this data. Of the 307 programmes sent a questionnaire for that year, 29 programmes gave start and finish numbers for patients with depression scores of over 8 or more. The results from the survey showed that 885 [16.7%] of 5299 patients scored 8 or more at the start of CR compared with 320 [6.0%] at the finish (Evans 2006). However, these data should be interpreted with caution. The number of responses was small; the survey did not ascertain the timing of assessments; and it is unlikely that baseline measures were all collected during the same time frame post event.

In the current study the proportion of patients with symptoms suggestive of either clinical depression or borderline depression at the second psychological assessment performed at the end of the Phase III CR programme had decreased from 15.2% to 4.4%. Just over 1% remained in the clinically depressed category and 3.3% were in the borderline category. Changes in depression scores during the CR programme were shown to be significant [Table 10:5 page 275]. Depression scores of participants in this

study over a three month period decreased by 33% between the assessments at the start and end of CR.

One other study has looked the effect of depression on morbidity in exercising coronary patients (Milani et al 1996) but there is no comparable study of the effect on mortality. In Milani's study there is a greater fall [54%] in depression over the course of the 3 month CR programme which may be explained by the greater number of exercise sessions attended by participants and by the fact that he used a different instrument to measure depression.

In common with other researchers I found that the depressed patients were less fit, less likely to complete CR, more likely to be smokers and have greater co-morbidity [Table 10.9 page 284 ] (Glazer et al 2002; Oldridge et al 1983; Turner et al 2002).

#### **12.4.6 Completion Rates**

In the present study there were 660 [24%] participants who failed to complete the CR programme [Figure 10:1 page 261] for a variety of reasons: they underwent cardiac surgery, became ill, died, moved house, had transport problems, or went back at work. Our non-completion rates were similar to the rates of 22% and 25% that have also been reported (Fioretti et al 1988; Vanhees et al 1995) but greater than Kavanagh's rates of 4.8% for males and 4.3% for females (Kavanagh et al 2002; Kavanagh et al 2003).



As was expected, and has been reported previously, the group who did not complete our programme was significantly different from the group who did [Table 10:2 page 264]; they were more likely to smoke, were also significantly more anxious, more depressed and less fit ( $p < 0.001$ ). They were also likely to live in areas of greater deprivation ( $p < 0.001$ ). The characteristics of people who do not complete CR have been studied by several researchers who have also found that non-completers were more anxious, depressed and less fit (Blumenthal et al 1982; Ladwig et al 1994; Oldridge et al 1983) and reported that they lived in more deprived areas (Lane et al 2001).

#### **12.4.7 Mortality**

During a follow-up period of almost 13 years [median 6.4 years] there were 451 deaths out of the 2,714 study participants [16.6% of the cohort], of which 277 deaths were from cardiovascular causes and 219 of the cardiovascular deaths were from coronary heart disease [Figure 11:1, page 294]. The all-cause death rate for females was 24.7 per 1000 person years, very similar to that of the males at 25.1 per 1000 person years. This compares with an all-cause death rate from Vanhees' younger male cohort of 14.3 per 1000 person years. For cardiovascular deaths in my study the figures were again very similar between the sexes at 14.9 for females and 15.5 for males.

#### **12.4.8 Mortality and fitness**

This study has found that an increase in fitness level for those in the lowest fitness category was associated with a reduced risk of death. For each one ml/kg/min increase in fitness level there was an 11% reduction in cardiovascular mortality [Table 11:21 page 322]. Only one previous observational study has assessed the effect of change in fitness level in CR on long term mortality (Vanhees et al 1995). Vanhees showed that cardiovascular mortality decreased by 2% for each 1% increase in  $VO_{2peak}$  and this was independent of the initial fitness level. This is equivalent to an 8.4% reduction in cardiovascular mortality for each one ml/kg/min increase in fitness.

One randomised controlled study of physical fitness and survival has also examined this relationship (Dorn et al 1999). This study, which I described in Chapter 4 page 73 [Tables 4:4a and 4:4b], followed up 651 low risk males post infarction for 19 years. The researchers reported an 8-14% reduction in all-cause mortality for each one MET gained in fitness. This is equivalent to a 3% reduction in all-cause mortality for each one ml/kg/min increase in fitness. Again, initial fitness level did not influence this finding.

It is not clear why my findings differed from those reported by both Vanhees et al and Dorn et al. For the low fitness group in my study failure to increase fitness was associated with greater risk and conversely increasing response to exercise was associated with a reduction in mortality. The probable



explanation for this was that those with the worse disease were unable to exercise sufficiently to increase their fitness level. They were likely to be patients who had left ventricular dysfunction and therefore a reduced ability to increase their fitness level.

The mortality rate in those with medium and high fitness levels in my study was much lower, indicating that these patients had better left ventricular function [Tables 11:1 and 11:2 page 294] which may explain why the association between mortality and changes in fitness was not seen.

#### **12.4.9 Mortality and depression**

Over the last 10 years several researchers have examined the effect of depression on mortality in people with coronary heart disease. In this study the hazard ratios of baseline depression for all-cause deaths [Tables 11:6 page 299 and 11:13 page 313] was 1.56 [95% CI 1.06,2.27] unadjusted, and when adjusted for age, gender, whether the CR was completed or not, the reason for referral to CR and co-morbid illness was 1.60 [95% CI 1.09,2.35]. For cardiovascular deaths [Tables 11:8 page 300 and 11.13 page 313] this was 1.68 [95% CI 1.05,2.69] unadjusted and 1.79 [95% CI 1.11, 2.87] adjusted for the same confounders.

In a meta-analysis Barth et al were the only reviewers to report studies with a follow up period beyond 5 years [Chapter 5 page 119] (Barth et al 2004). Most of the patients in these studies had suffered an acute myocardial

infarction and the majority of patients were male. Mean ages of patients ranged from 54 to 74 years, with a minimum age of 19 years and a maximum of 90 years. Results for six of the studies with longer follow periods were adjusted for a variety of confounders, which included age, gender, smoking, hypertension, hyperlipidaemia, diabetes mellitus and body mass index [HR 1.76 95% CI 1.27,2.43]. Five of these studies reported cardiovascular as opposed to all-cause mortality as an outcome. However, age and gender were the only covariates common to both my study and the studies included in the meta-analysis.

Two studies in Barth's meta-analysis had similarities with this study. Both were performed in the United Kingdom and followed up hospitalised myocardial infarction survivors (Lane et al 2002; Mayou et al 2000). Mayou used the HADS with a cut off point of 19 [as opposed to 18 in this study] to assess depressive symptoms in 344 patients [mean age 63 years, 27% female] who were followed up for 18 months. The odds ratio was reported for all-cause deaths but not cardiovascular deaths, OR 1.6 [CI 0.43,5.95] at 6 months and OR 1.64 [CI 0.64,4.20] at 18 months. On the other hand, Lane used the BDI to assess depression in 288 participants [mean age 63 years, 29% female] with a follow up of 3 years and reported an unadjusted odds ratio as 1.15 [CI 0.49,2.70] at the end of the first year of follow-up. The odds ratio decreased to 0.84 [CI 0.3,1.91] by 3 years.



Neither of these studies showed depressive symptoms to be predictors of survival when depression was assessed during the acute phase of a myocardial infarction. This differs from my findings where a baseline depression score of greater than 10, before adjusting for fitness, was associated with an increase in both all-cause and cardiovascular mortality when depression was assessed several weeks after the acute event or procedure. It may be that in-hospital depression which improves spontaneously after discharge is not associated with a worse prognosis while persisting depression is. I discuss this point again later in this chapter. The follow-up period was also much shorter in these studies than the follow up of nearly 13 years in this study, which may also explain the differences between the three studies.

My study did not have sufficient power to show any effect on changes in depression scores between the start and end of CR as the depressed group of patients was small [67 participants] with just 29 deaths. No other observational study has examined the effect of change in depression on mortality.

### ***12.5 Implications for clinicians and policy makers***

There are six findings from this research study which could be used to modify policies to improve the outcome for coronary heart disease patients who are enrolled in CR programmes. Three of these findings relate to estimated levels of cardiorespiratory fitness. Firstly, a higher fitness level [an estimated

VO<sub>2peak</sub> of 15ml/kg/min or more] was associated with improved survival. Secondly, improving the fitness level for patients with a low fitness level [an estimated VO<sub>2peak</sub> of less than 15ml/kg/min] was also associated with better survival. Thirdly, a low fitness level predicted an increased risk of non-completion of the CR programme.

There are three findings that related to our assessment of depression. The patients with scores of over 10 on the HADS depression subscale had overall poorer survival than those who scored 10 or below, but this effect was no longer significant after controlling for fitness. However, a high HADS Depression score also predicted increased risk of non-completion of the CR programme. Finally the HADS identified a very low prevalence of depression in the cohort in this study.

#### **12.5.1 Policies related to exercise and fitness testing**

A formal assessment of fitness level should be carried out at the start and the finish of the CR programme to enable a level of fitness to be estimated for each patient. From an annual BACR survey of CR programmes in the United Kingdom we know that few CR programmes measure fitness before CR and very few both before and after programme, probably due to the lack of financial or staffing resources. In the year 2000, 26 [10%] of centres that responded to the relevant section of the BACR questionnaire, reported that they performed exercise tests before and after CR. Of these only 8



programmes were able to provide data supporting this statement (Bethell et al 2004).

Initial fitness testing of coronary patients is important for a number of reasons. It acts as a guide to help practitioners individualise the exercise prescription. For example patients can be set an appropriately targeted heart rate range to achieve whilst exercising and be encouraged to exercise at a suitable level commensurate with ability and safety. My research confirms that fitness testing performed at entry to CR adds to the process of risk stratification for each individual and helps to identify the higher risk patients as well as those who are most likely to fail to complete CR. Low fitness level patients need more careful monitoring and a more prolonged course of exercise in Phase III than their fitter counterparts. This is for two reasons. Firstly, they are at higher immediate risk and secondly giving them a longer course of exercise should result in greater improvement in exercise tolerance and consequently perhaps improve their prognosis. After the finish of the programme these patients also need more careful follow up. Their higher risk status should be reported back to the general practitioners and cardiologists so that more frequent long term monitoring can be used.

Fitness testing at the end of an exercise programme is also important. It measures the overall effectiveness of the exercise programme and provides data for audit purposes. For the individual patient it provides a measure of the success of their efforts, which may motivate them to continue exercising

in the longer term. My study adds to this the finding that those who start with low fitness but improve, have a better prognosis than those who do not. Repeating the fitness test at the end of the exercise programme therefore helps to identify the patients who remain in a higher risk group at the end of CR and who may thus require further attention, such as a clinical cardiological review, change of treatment, longer medical surveillance or/and long term monitoring.

By spending less Phase III time and fewer resources on the lower risk patients with high fitness levels, more time would become available for the needful higher risk patients, and the level of provision of CR to include more high risk individuals could be developed.

#### **12.5.2 Policies related to psychological health**

A psychological assessment at the start and end of the CR programme is also invaluable. It identifies those patients with an overall worse prognosis and those less likely to complete the programme. It provides data for audit of the service and may help to monitor the effectiveness of psychological components of the CR programme. In a BACR survey of CR programmes in the United Kingdom (Bethell et al 2000) only 17% of programmes had documented data at baseline on the psychological health of their CR patients and even fewer at the end of the Phase III programme. My findings indicate that patients with high HADS depression scores should be monitored carefully during Phase III. Moreover, after the finish of the Phase III



programme, like the low fitness group, they need careful follow up in the long term. Their general practitioners should be alerted to their higher risk status if they have high depression scores so that appropriate treatment can be offered.

Identification of depression by the HADS depression score indicates a low prevalence of depression in this cohort. We did not measure depression until the start of Phase III, several weeks after the acute cardiac event or procedure. There may be two reasons to explain the low prevalence of depression in this study. During Phase 1 we may have simply missed inviting some depressed patients to join the programme while others may have failed to take up the invitation because of their depression. Alternatively, the patients depressed during the early stages of their coronary illness may have undergone a spontaneous recovery during the few weeks prior to starting their Phase III exercise programme as was found in both the ENRICHD (Blumenthal et al 2004) and SADHART studies (Glassman et al 2002).

There are two issues concerning psychological assessment. Firstly, which type of instrument should be used to measure depression and secondly at what stage of the patients' illness is this best done.

Since the HADS may have been a relatively insensitive measure of depression in this cohort of patients consideration should be given to

assessing depression with other instruments. The psychometric properties of screening instruments vary. The BDI for instance has 7 out of 21 items associated with somatic symptoms whereas the HADS has none. This means that the assessment with the BDI may pick up symptoms such as fatigue or anhedonia which are common to both newly diagnosed myocardial infarction patients as well as patients who are depressed. No systematic reviews on the psychometric properties of depression screening instruments for coronary heart disease cohorts have been published to date (Thombs et al 2007).

The timing of the first psychological assessment and early detection of depression when it is present is important (Doyle et al 2006; McGee et al 2006). Since the HADS may also have been a relatively insensitive measure of depression in this study when depression status was measured at the start of Phase III, it may be useful to initially assess coronary patients during Phase I, in the earlier stages of their illness. Extra effort can then be made to ensure that coronary patients found to be depressed during hospitalisation are offered treatment for depression to improve quality of life, as well as appropriate secondary prevention whether they choose to participate in CR or not.

I discuss both these points again in the following section of this thesis.



## **12.6 Future Research**

### **12.6.1 The importance of baseline fitness**

Higher fitness even after adjusting for age, gender, reason for referral to CR, whether CR was completed or not and co-morbidity is associated with a better survival. There are several possible reasons for this. Firstly, the fitter patients are likely to have better left ventricular function than the unfit. Secondly, they may also have less residual coronary narrowing. Thirdly, they may be also less subject to the consequences of ventricular arrhythmias. Lastly, those with high fitness levels may be protected because they were more physically active and therefore fitter before the index coronary event.

Unfitness therefore in the coronary patient is a marker for being either very sick with poor overall cardiac function or the result of many years of a sedentary lifestyle. It is likely that co-morbidity, non-adherence to exercise regimes and other preventative measures also contribute to low fitness levels.

There are several components of exercise programmes that influence cardiorespiratory fitness. For example the intensity and frequency of the prescribed exercise, the duration of the programme, the use of home exercise programmes, adherence to prescribed home exercise, the ability to perform an adequate exercise prescription and the extent of co-morbid illness which may limit the amount of physical activity performed. The latest NICE<sup>i</sup>

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<sup>i</sup> NICE - The National Institute for Health and Clinical Excellence

clinical guideline on secondary prevention post myocardial infarction, based on the best available evidence, suggests that CR patients should be advised to undertake regular activity sufficient to increase exercise capacity. It states that patients should be advised by health professionals to increase their exercise capacity by exercising for 20-30 minutes regularly at an intensity sufficient to bring on mild breathlessness (Cooper et al 2007).

The average number of supervised exercise sessions undertaken by treatment patients in the randomised controlled trials in the Cochrane review was 48. Most of the randomised controlled trials reported on patients who have attended several sessions of supervised exercise per week (Vanhees et al 1995, Milani et al 1996). The weekly frequency of supervised exercise may go a long way to increasing the individual's fitness. The National Service Framework for Coronary Heart Disease (DOH 2000) recommended CR patients attend at least 12 sessions of exercise during Phase III, and the SIGN Guideline recommended 16 (SIGN 2002). In practice, many programmes in the United Kingdom offer even fewer sessions than this (Brodie et al 2006) and little is known about the intensity of individualised exercise programmes in routine practice or through research.

A large scale multicentre cohort study within the United Kingdom is needed to monitor fitness levels in CR using measured  $VO_{2peak}$  at the start and finish of the CR programme. This study could concentrate on the relative importance of factors known to influence fitness and prognosis including the severity of coronary disease, co-morbid illnesses including the more complex



co-morbidities, and the effect of non-adherence on outcomes of all eligible CR attendees. It should investigate treatments that are likely to be accessible in routine care and therefore helpful to policy makers, as opposed to unrealistic treatments that have been available in the various studies conducted to date. In addition, it could consider the role of homework, individualised goal setting and targets which may be cheaper and effective ways to improving fitness than attendances at supervised sessions. The outcomes of the shorter programmes versus the longer ones could also be compared.

#### **12.6.2 The importance of baseline depression**

My literature review revealed that most studies of depression and coronary heart disease focussed on patients post myocardial infarction. Little is known about the natural history of depression in patients who have undergone revascularisation procedures. Moreover, different instruments give a different prevalence of depression in coronary patients, as does the timing of the measurement. An observational study following up patients post revascularisation as well as post myocardial infarction, who have been assessed with several instruments such as the HADS, the BDI, the Cardiac Depression Scale (Hare and Davis 1996) or the Patient Health Questionnaire PHQ – 9 (Kroenke et al 2001) at different times would identify the instrument and timing which gives the most sensitive and specific prediction long term prognosis. It would be possible to screen patients initially during the first stage of illness to identify depression, and provide more in depth screening

with subsequent follow up, monitoring and treatment in the community by general practitioners as required for those found to be depressed.

### **12.6.3 Treating depression and prognosis**

There have been three studies [Chapter 7] of the effect of antidepressant treatments on prognosis following acute coronary events. But these have failed to show a benefit in either coronary prognosis or depression status.

The ENRICHHD study (Berkman et al 2003) looked at the effect of treating depressed patients with cognitive behavioural therapy or usual care. Although depression status was found to improve during the first 6 months of the follow up period, this effect was lost by 30 months. There was also no difference in event-free survival between the two groups that were studied. The SADHART study (Glassman et al 2002) investigated the safety of the antidepressant medication sertraline in post myocardial infarction patients. Although the intervention group who received sertraline as a treatment rather than placebo suffered fewer cardiovascular events, the longer term effect of sertraline was not studied. The third study followed up depressed myocardial infarction patients who were treated with a variety of antidepressant therapies over an 18 month period. It also failed to provide evidence that treating depression improved either cardiac prognosis or long term depression for either the intervention group or those who had received usual care (van Melle et al 2007).



However even though depression in acutely ill coronary patients appears to resolve spontaneously over time, it is nonetheless important perhaps to identify and treat it, in order to improve the quality of life of depressed patients during the initial recovery period. Future studies therefore should focus on determining which treatments are able to achieve this. Such treatments may be different to those known to be effective in people without coronary disease. Future challenges for researchers include carrying out studies that focus on understanding the mechanisms that give rise to poorer prognoses in depressed coronary patients, as well as whether certain aspects of depressive illness are more detrimental than others to cardiac outcomes.

## ***12.7 Conclusions***

In summary, this study has shown that initial levels of cardiorespiratory fitness and baseline depression scores are associated with prognosis in coronary heart disease patients who have attended an exercise-based CR programme. It is important that those who care for coronary patients are aware of these issues to allow for better targeted treatment for those coronary patients who are found to be at highest risk.

## Chapter 12: References

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